Mechanism of action and therapeutic targeting of microglia in autism spectrum disorder

Yangming Zhang†, Yuqiao Xie†, Zishuo Cheng†, Yanran Zhang, Wenting Wang, Baolin Guo*, and Shengxi Wu*
Department of Neurobiology, School of Basic Medicine, Fourth Military Medical University, Xi’an, Shaanxi, China

Abstract

Autism spectrum disorder (ASD) is a complex mental illness with a high incidence and considerable impact. More than half of the affected individuals have self-harm behaviors, resulting in high mortality and morbidity. The impact of ASD on education and employment opportunities, the need for family care and support, as well as the burden on families and society is enormous. The underlying pathogenesis of ASD is still unclear, and effective interventions are lacking. Microglia are key immune cells in the central nervous system (CNS), and they function far beyond classical innate immunity, as they can affect normal neuronal activity by secreting cytokines and pruning synapses through phagocytosis. On the one hand, the abnormal activity of microglia may contribute to the development of ASD; on the other hand, it provides a potential target for intervention and treatment. In this review, we comprehensively analyze the mechanism of action of microglia in ASD development and summarize the current methods for targeting microglia in treating ASD.

Keywords: Autism spectrum disorder; Microglia; Neuroinflammation; Cellular immunotherapy

1. Introduction

Autism spectrum disorder (ASD), also known as an autistic disorder, is a developmental brain disorder. The main symptoms are social handicaps, communication disorders, narrow interests, and stereotypical repetitive behaviors[1]. ASD begins before the age of three and manifests significantly thereafter. The vast majority of children require long-term rehabilitation training and special education support. One-third of individuals with ASD may remain mute all their lives, one-half have no sense of safety or need to be restrained in their actions, nearly two-thirds of children with ASD experience bullying, and approximately one-third engage in self-harm behaviors, such as head banging, arm biting, and skin scratching[2]. The average cost for individuals with ASD is approximately $60,000/year throughout their childhood[3] and increases with the onset of intellectual disability. According to the latest screening data on ASD from the Centers for Disease Control and Prevention, one in 54 children is diagnosed with ASD, with a 24% increase in prevalence from 2016 to 2018[4].

A century ago, microglia were first recognized as a distinct cell population in the central nervous system (CNS)[5] and were primarily thought to be phagocytes responsible
for removing debris during CNS development and in pathological conditions. Microglia-mediated immune inflammation was believed to affect the stability of the CNS\textsuperscript{[8]}. With the advances in genetic technologies and single-cell analysis, the connection between microglia and neurons has become more apparent. Besides being central to the inherent immune response, microglia are involved in a variety of neuropsychiatric diseases; functional abnormalities of microglia have been confirmed in anxiety, depression, and other mental disorders. Therefore, the mechanism of action of microglia in mental illness is one of the trending topics in current research. The modulation of neuronal activity by microglia is evident in many brain diseases\textsuperscript{[7]}.

The dysfunction of microglia may be one of the underlying mechanisms in ASD\textsuperscript{[9]}. Aberrant activity of microglia, abnormal levels of associated inflammatory factors, and certain cellular pathways have been observed in autistic patients and animal models. Both genetic and environmental factors that affect microglia may be involved in the etiology of ASD\textsuperscript{[9]}. The deletion or amplification of certain genes may cause ASD, and changes in the peripheral environment may affect microglia, further aggravating autism-like behaviors.

In this review, we propose that microglia are related to the development and progression of ASD. Several widely accepted theories on the etiology of ASD and ASD models are discussed. We focus on the mechanistic role of microglia in ASD from the perspective of phagocytosis and synaptic pruning, which affect neuronal activity, through the release of inflammatory factors and their influence on inflammatory pathways. We also summarize several intervention approaches for ASD by modulating microglia and analyze the current challenges in treating ASD by regulating microglia in hope that this review will make modest contributions to the early diagnosis and treatment of ASD.

2. Etiology of ASD and its pathogenesis

The etiology of ASD is still unknown. Epidemiological studies, screening for many possible risk factors, could not identify a direct contributor to the development of ASD. Although the etiology of the disease is not fully understood, genetic factors, manifested as deletion or abnormal insertion of specific genes, and gene-environment interactions might lead to autistic-like behaviors. For example, genes such as CNTNAP2, NLGN3, and SHANK3 have been shown to be associated with ASD. Cntnap2 knockout mice, Nlgm3 knock-in mice, and partial knockout of Shank3 gene are the common genotypes used to construct ASD animal models. In addition, maternal immune activation (MIA) is believed to be a cause of ASD\textsuperscript{[10]}. Studies have demonstrated that infection during pregnancy, especially in the first trimester, is a risk factor for the development of ASD in offspring\textsuperscript{[11]}. MIA models were induced using polyribosinosine polyribocytidylic acid (poly[I: C]), lipopolysaccharides (LPS), valproic acid treatment, simulated viral and bacterial infections, as well as other environmental factors to activate the maternal immune system\textsuperscript{[12]} and test possible autistic-like behavioral manifestations in offspring (Figure 1).

Stimulation of certain physicochemical factors during pregnancy also leads to a significantly increased risk of ASD in offspring. It has been reported that exposure to valproic acid during pregnancy increases the probability of ASD in offspring by 50\textsuperscript{th}\textsuperscript{[13]}. Studies of the early pregnancy diets have shown that propionic acid salt might accumulate in the gastrointestinal tract of pregnant women who consume processed foods that are rich in propionate. Propionate can pass through the placental barrier, bind with G-protein receptors 41 (GPR41) on glial progenitor cells, and cause impaired neural differentiation. Furthermore, the expression of downstream phosphatase and tensin homolog deleted on chromosome 10 (PTEN) is inhibited, and protein kinase B (PKB) pathway is activated to promote the proliferation and differentiation of glia. Subsequently, glial cells continue to produce inflammatory cytokines and release glial fibrillary acidic protein (GFAP) after maturation, thus affecting the development of the fetal nervous system.

3. Role of microglia in ASD

Microglia, the innate immune cells of the CNS, have high plasticity and can react rapidly during pathological processes. Microglia have been implicated to play a crucial role in the development of ASD associated with CNS inflammation\textsuperscript{[14]}. Recent advances have shown that microglia function far beyond the classical innate immune response and are involved in various processes, such as neuronal excitation, synaptic pruning, and remodeling\textsuperscript{[15,16]}. A growing number of studies have demonstrated that the biological role of microglia has a close association with ASD\textsuperscript{[17]}. As early as 2005, the significant activation of microglia and astrocytes in the brains of autistic patients has been reported by Diana \textit{et al.}\textsuperscript{[18]}. Since microglia activation is the main cellular response to CNS dysfunction, it is conceivable that abnormal glial cell is inextricably linked to ASD.

3.1. Microglia mediate abnormal neuronal synapse pruning/clearing

Microglia are involved in the pruning and clearance of neuronal synapses. Rosa \textit{et al.}\textsuperscript{[19]} have reported the...
importance of the active engulfment of synaptic structures by microglia during neuronal development to maintain normal neuronal functions\[20\]. In their physiological state, microglia have a role in removing pathogens and maintaining CNS stability, directing the remodeling of brain cells after infection, removing debris in pathogenic infection, as well as restoring affected intracellular and extracellular connections. In addition, 50% of neurons undergo programmed cell death during normal brain development, and microglia dispose of these neuronal corpses through phagocytosis. However, under specific circumstances, the impairment of microglial functions, which include phagocytosis and pruning, may lead to abnormalities in neuronal function\[21\], thus resulting in certain autistic manifestations.

At the postsynaptic level, previous studies have identified significant neurological changes in the brain of ASD patients, such as neuronal overgrowth and microglia activation in the frontal cortex\[18\]. Animal experiments have revealed that autistic mice have significantly higher dendritic spine densities\[22\], which could be the result of pruning abnormalities and decreased microglial ability to phagocytose synapses. In addition, the impaired synaptic connections between neurons following infection, which are caused by microglia, may also contribute to ASD\[23\].

At the presynaptic level, several studies have shown that the balance between excitatory (E) and inhibitory (I) synapses is disrupted in ASD patients. Appropriate pruning of synapses by microglia is vital to ensure the function of excitatory and inhibitory neurons. Therefore, the aberrant pruning effect of microglia on the E/I balance may be one of the pathological reasons for ASD. It has been confirmed in animal experiments that abnormal microglial phagocytosis will break the balance of E-I synapses and eventually lead to the development of neurodevelopmental disorders and advanced brain dysfunction, such as Alzheimer’s disease and ASD\[24\]. However, the role of E/I signaling in ASD is still controversial. Some studies have found that the function of excitatory synapses is inhibited in \textit{Shank2} - and \textit{Shank3}-deficient mice\[25\]. In contrast, other studies have shown that the synaptic E/I balance in the hippocampus inclines toward excitability\[26\]. Recent studies have observed the preferential elimination of excitatory synapses by microglia in pathological and physiological brains of mature rats. The impairments of microglia in pruning excitatory synapses would result in a predominance of excitatory signaling compared to inhibitory signaling in the ASD brain. The intervention of the abnormal pruning process will be a practical approach for ASD treatment in the future\[16\].

3.2. Microglia contribute to the progression of ASD by mediating inflammatory pathways and cytokines

Microglia are key immune cells of the CNS, and the neuroinflammation that is mediated by microglia is
centrally involved in CNS injury and disease processing. Microglia can be categorized into two phenotypes, the pro-inflammatory M1 type and the anti-inflammatory M2 type. M1 microglia, which induce neurotoxicity, can secrete pro-inflammatory cytokines and chemokines such as interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α. The neuroprotective M2 phenotype contributes to regulating inflammation with specific cytokines, such as IL-10 and transforming growth factor (TGF)-β, as well as neurotrophic growth factors, such as brain derived neurotrophic factor (BDNF) and glial cell-derived neurotrophic factor (GDNF). The balance of M1/M2 paradigm underlies different neuropathological conditions in ASD and is essential for CNS hemostasis. It is widely believed that an abnormal inflammatory response induced by M1 microglia may be an etiology of ASD. Microglia regulate neuroinflammation through specific inflammatory pathways, such as nuclear factor kappa B (NF-κB), mitogen-activated protein kinase (MAPK), IL-1β, IL-6, IL-8, IL-17, and TNF. The dysregulation of these pathways will affect neuronal activity and result in ASD-like symptoms.

3.2.1. Inflammatory pathways

The inflammatory pathway of NF-κB that is regulated by microglia plays an important role in mediating immune response. The initiation of the NF-κB signaling pathway and the transcription of cytokines involved in directing the immune response are required following an infection to clear the invading pathogenic bacteria. Therefore, the NF-κB signaling pathway is closely associated with inflammatory diseases and regulates the expression of genes encoding immune response proteins. Inflammatory cytokines, infection markers, or stress-activated protein kinases can induce the activation of the NF-κB pathway. Within the CNS, the abnormal activation of the NF-κB signaling cascade leads to an abnormal expression of pro-inflammatory cytokines, which may disrupt normal neuronal activity. A large number of literature works have reported that the activation of microglial NF-κB pathway may be involved in the regulation of ASD.

The MAPK signaling pathway also plays a key role in inflammation and can be activated by cytokines, stress mediators, and inflammatory markers. Microglia activation can also induce the MAPK signaling cascade, which is primarily influenced by the activation of toll-like receptors during inflammation, resulting in the phosphorylation of transcription factors. Once phosphorylated, the transcription factors translocate to the nucleus and transcribe genes encoding pro-inflammatory cytokines, such as IL-6 and TNF-α, thus promoting a neuroinflammatory environment and leading to an increased risk of ASD. Besides, IL-6 cytokines form a positive feedback loop by activating MAPK signaling, thus exacerbating inflammation.

3.2.2. Inflammatory cytokines

The increased release of inflammatory factors is closely associated with the development of ASD. The expression of inflammatory molecules, such as IL-1β, IL-6, IL-8, IL-17, and TNF, has been found to be elevated in ASD, and it has been suggested that the severity of the ASD phenotype might be positively correlated with the pro-inflammatory cytokine concentration. Among them, pro-inflammatory cytokines IL-1β and IL-6, released by activated microglia, might have a role in neuronal damage and significantly affect ASD. In addition, maternal infection or inflammatory immune activation during pregnancy may drive microglia activation and promote pro-inflammatory cytokine release, which would, in turn, exacerbate the inflammatory response.

IL-1β is a key pro-inflammatory cytokine that is involved in various autoimmune inflammatory responses and cellular activities, such as cell multiplication, differentiation, and apoptosis. The synthesis and release of IL-1β are tightly regulated, and its expression is upregulated in acute inflammatory, chronic inflammatory, and autoimmune inflammatory diseases. Microglia can produce large amounts of IL-1β within the CNS. Abnormal IL-1β levels may be responsible for neurological deficits of the brain in ASD. In a study of serum extracellular vesicles in children with ASD, Tsilioni et al. found that the IL-1β levels in these children were remarkably higher than the controls following microglia activation. Another study found elevated IL-1β levels in children with degenerative ASD and that IL-1β regulates the proliferation of neural precursor cells, suggesting that elevated IL-1β levels in the brain of ASD patients may alter neuronal development and affect postnatal neural development.

IL-8 is a pro-inflammatory cytokine, secreted by various cells, including macrophages and microglia. IL-8 functions primarily as a neutrophil chemotactic factor in the blood. This pro-inflammatory cytokine that is released from microglia increases in response to pro-inflammatory stimuli. Elevated peripheral IL-8 levels have been observed in psychiatric disorders, such as major depression, bipolar affective disorder, schizophrenia, sleep disorders, ASD, anxiety disorders, and dementia. In a clinical study conducted by Bryn et al., serum IL-8 concentrations were significantly elevated in children with ASD compared to healthy controls; this finding validates the role of peripheral IL-8 associated with microglia in ASD. Another study found that ASD patients have higher IL-8 levels in the...
Microglia in Autism Spectrum Disorder

Microglia in autism spectrum disorder

3.3. Microbial-gut-brain axis and microglia

In the past few decades, the “microbial-gut-brain axis” has garnered widespread attention from researchers, leading to the discovery of the two-way communication between the gut and brain through pathways involving neural, endocrine, and immune systems. Intestinal microbiota is extensively involved in each pathway of the brain-gut axis, influencing neurodevelopment, cognition, and behavior by regulating the two-way communication between the gut and the CNS. Studies have shown that gut microbes play an important role in brain function. Many studies have explored the effect of intestinal microbes on microglia-associated neuroinflammation and found immune abnormalities in the gastrointestinal tract of autistic patients, such as increased intestinal immunoglobulin (Ig) G, intestinal CD8 lymphocyte, and T-cell infiltration in the mucosal lamina propria. The deposition of IgG1 and IgG4 has been observed in the basement membrane of intestinal epithelium, along with an increased production of TNF-α in intestinal lymphocytes. Peripheral circulating immune cells may penetrate the blood-brain barrier (BBB) and subsequently affect neurons and glial cells, thereby perpetuating the immune response. Microglia respond to local signals within the brain and receive inputs from the periphery, including the gastrointestinal tract. There is evidence showing altered microbial community composition in nervous system diseases. Recent clinical research has revealed that gut microbes play a critical role in regulating microglial cell maturation and function.

Using the adenoviral gene delivery approach, Wei et al. developed a mouse model that overexpressed IL-6 centrally and confirmed that the overexpression of IL-6 is an important mediator of autistic-like behaviors. When IL-6 levels were elevated in the brains of mice, autistic-like behaviors were observed. Elevated IL-6 levels have also been reported to cause abnormal changes in the shape, length, and distribution pattern of dendritic spines, suggesting that elevated IL-6 levels may mediate ASD-like behaviors through an imbalance of neural circuits and impairment of synaptic plasticity. In the CNS, astrocytes, microglia, neurons, and endothelial cells of the cerebral microvascular system are the cellular sources of IL-6, and its levels are significantly affected by abnormal microglia activation.

4. Therapeutic strategies targeting microglia

In the previous section, we discuss the key roles microglia play in the neuroinflammatory process of ASD. As a dynamic cellular mediator in the CNS, microglia can disrupt the balance of the nervous system by affecting the microenvironment and deranging the expression of important neuroinflammatory molecules. Preclinical assessment is anticipated to benefit from treatments targeting microglia dysfunction.

4.1. Microglia and inflammatory interventions

Microglia are the primary immune cells involved in neurodegenerative diseases of the CNS, such as ASD. Microglia express various immune receptors that secrete numerous cytokines and chemokines. The malfunctioning of these molecules in the pathologic signaling pathways of ASD provides neuroscientists and clinicians with potential treatment targets.

4.1.1. Targeting microglia in synapse development

Insufficient pruning of weak or nonfunctional synapses by microglia can perturb neurodevelopment due to decreased levels of complement receptor 3 (CR3) or complement component 3 (C3). Microglia regulate synaptic plasticity...
Microglia in autism spectrum disorder

through the secretion of reactive oxygen species (ROS) and BDNF, which engages the Trk receptors that modulate the activities of various synapses. Synaptic pruning by microglia is impaired if CX3CR1-CX3CL1 interactions are imbalanced\(^{[61]}\). By blocking inflammatory microglia functions, humanized antibodies or other reagents that target the aforementioned molecular markers may have beneficial effects. The inverse functions of M1/M2 microglia phenotypes provide us with a promising therapeutic idea that emphasizes on the balance of polarizations. Shifting the polarization from M1 to M2 helps in neural regeneration and regulates neuroinflammation in neurodevelopmental diseases, like ASD. The simultaneous inhibition of M1 microglia and acceleration of M2 microglia transformation might be useful for treating ASD\(^{[62]}\). However, due to the lack of animal experiments using M1 depressants like cyclooxygenase inhibitors, and anti-inflammatory drugs like aspirin, for treating ASD, the eligibility and availability of these drugs still require further testing. Recently, the research focus has been on microglia autophagy. It has been reported that the loss of mammalian target of rapamycin (mTOR)-dependent macro-autophagy can lead to ASD-like spine densities and a decrease in presynaptic markers, like light chain protein 3-II (LC3-II)\(^{[63]}\); additionally, malfunctioning autophagy can also be induced by infected microglia\(^{[64]}\). Hence, the potential relationship between mTOR-dependent autophagy and infected microglia may provide researchers with interesting targeting methods (Figure 3).

4.1.2. Targeting microglia in maternal immune activation

Infection during prenatal period induces pro-inflammatory cytokines, such as TNF-\(\alpha\), IL-6, and IL-\(\beta\), causing neuroinflammation effectors that activate microglia\(^{[65]}\). Coadministration of anti-IL-6 and -IL-1\(\beta\) antibodies has also been demonstrated in certain animal models. Suramin has shown to be effective in improving core ASD behaviors by recovering dysregulated purinergic metabolism in the poly I: C-exposed MIA model of adult ASD mice\(^{[66]}\) (Figure 4).

4.2. Metabolic deficiency and microglia abnormalities

Omega-3 polyunsaturated fatty acids (n-3 PUFAs) are essential in maternal diet. A deficiency of n-3 PUFAs alters the offspring’s microglia lipid composition and oxylipin signature, which are implicated in inflammation, resulting in microglia polarization toward a phagocytic phenotype, possibly by the overexpression of 12-hydroxyeicosatetraenoic (12-HETE)\(^{[67,68]}\). Phagocytic

Figure 2. Involvement of microbial-gut-brain axis in autism spectrum disorder (ASD) development. The microbial-gut-brain axis plays a role in ASD development by regulating body immunity. On the left is the physiological state: the secreted metabolites from intestinal flora activate the peripheral immune system, causing the production of inflammatory factors, which reach the central nervous system through the BBB and act on microglia for normal phagocytosis and pruning. On the right is the pathological state: the integrity of intestinal epithelial cells is destroyed, and the metabolites entering the periphery are significantly increased, enhancing the peripheral immune response, and affecting the activity and physiological function of microglia.
Advanced Neurology

Microglia in autism spectrum disorder

Microglia produce a cascade of neuroinflammation cytokines that impair spine refinement or synaptic pruning. Supplementing with n-3 PUFAs from weaning to adulthood has led to significant improvements in ASD-like social deficits in ASD mouse models. Therefore, fish-oil capsules, containing n-3 fatty acids, with vitamin E supplements may be one of the key treatments for ASD patients (Figure 3).

4.3. Gut-brain axis and microglia

The gut-brain axis plays an intrinsic role in brain homeostasis. Microbiome-microglia crosstalk research has generated novel therapeutic approaches for ASD patients. There have been reports of several microbiota metabolites that impact the physiological characteristics of microglia. As bacterial metabolites derived from microbial fermentation, the three main short-chain fatty acids (SCFAs) – propionate, butyrate, and acetate – can be beneficial or detrimental for ASD treatments. Using antibiotics against Clostridia and Bacteroidetes, the main producers of propionate can help prevent the increased activation of microglia. The treatment with butyrate or its byproducts generated by Clostridium butyricum promotes anti-inflammatory effects in microglia, contributing to the improvement of neuropsychiatric symptoms associated with ASD. It has been suggested that p-Cresol, which is derived from Blautia hydrogenotrophica and Clostridium spp., induces microglia activation and neuroinflammation. Recolonizing patients with various microbiota or feeding SCFAs can sufficiently modulate microglia activation and alleviate ASD syndrome.

5. Challenges

ASD is a psychosocial condition that persists throughout life. ASD patients experience social, speech, and behavioral changes that can severely disrupt their daily life and work. At present, there are many challenges in the treatment and prevention of ASD. Since the disorder cannot be cured, it becomes a lifelong problem for patients. Furthermore, the detection of ASD is not feasible at an early stage or through pregnancy screening. The diagnosis of ASD mainly relies on behavioral observations, and its symptoms cannot be detected under the age of three, thus missing the critical period of intervention.

MIA during pregnancy is one of the well-recognized mechanisms that have been successfully used to construct animal models. Altered cytokine expressions could facilitate the identification of ASD phenotypes and provide
Microglia in autism spectrum disorder

A timely analysis of gestational samples is an excellent opportunity for pathological diagnosis and future behavioral interventions in the early ASD childhood. However, the average age of ASD children at which atypical behaviors are first noticed by the parents is 4.6 years. This means that sample analysis during pregnancy may not be a suitable solution due to parental acceptance. Some animal experiments have shown promising results concerning therapeutic targeting T helper 17 (Th17) cells in preventing inflammation-induced ASD-like behaviors in offspring of susceptible mothers. However, the specific inflammatory factors that cause ASD are poorly understood, and most existing immunomodulatory tools are ineffective. There are still many challenges in reversing the pathological changes in gestation to ameliorate ASD-like behaviors in offspring; however, fostering routine sample analysis and clinical trials would help address these challenges.

Microglia are innate immune cells of the CNS. An important pathogenic mechanism of ASD is the decreased ability of microglia to engulf and prune unwanted synapses, resulting in CNS inflammation. A number of studies have demonstrated that microglia release IL-1β, IL-6, IL-8, and other inflammatory factors, and these factors are significantly increased in the peripheral blood and CNS of autistic patients. Insights into possible targets associated with microglia would aid the development of potential medical therapies for various CNS disorders. A recent study identified a novel pharmacological anti-neuroinflammatory agent and GIBH-130, for Alzheimer's disease through microglia-based phenotypic screening, the method by which novel favorable targets in ASD models may be introduced. Further studies are needed to confirm the specificity of inflammatory factor release and the intricate interactions between microglia and inflammation. Besides, glial cell modulation cannot be precisely controlled, and microglia modulation may have other adverse effects on the CNS, thus posing a challenge for ASD treatment.

6. Conclusion

Our work offers a summary of the main pathological mechanisms of microglia in ASD and several targeted therapeutic methods. There are limitations in the existing mechanisms, such as the ambiguous pruning preference for which type of synapses and the lack of explicit cause-effect relationship between studies, like MIA and microglia polarization. Focusing on new insights such as glial cell interactions and autophagy may bring promising results. As for effective interventions, most therapeutic methods are still...
in the theoretical stage and have not been translated from ongoing animal experiments to clinical trials. The precise regulation of microglia should be the focus of future research, but elucidating the explicit circuits still remains a priority.

The emphasis of future research on ASD should include a range of relevant mechanisms: (1) the involvement of microglia in the development of ASD, and the molecular mechanisms of microglia activation, which are crucial for precise intervention; (2) the modulation of cytokines secreted by microglia, including IL-1β, IL-6, and IL-8 in both peripheral blood and CNS of ASD patients, and the inflammatory pathways they participate in, since there might be association between the role of inflammatory factors and the abnormal phagocytic pruning by microglia; (3) the characterization of microglial activity and marker molecules in the early stages of ASD, which is crucial for the early identification and intervention of ASD.

Acknowledgment
Language editing was performed by editors of scientificmanuscriptediting.com. The schematic diagrams were prepared using FigDraw resources. The relevant authorization code is as follows: TUPUSd4c58, TARS9rc992, APSSRe7bbe, and iTART05260.

Funding
This work was supported by the Science and Technology Innovation 2030 Project of China (2021ZD0201005 to S.W.), the Natural Science Foundation of China (81730035 to S.W. and 62201699 to B.G.), and the Natural Science Basic Research Program of Shaanxi (2021JCW-13 to S.W.).

Conflict of interest
The authors declare that they have no competing interests.

Author contributions
Conceptualization: Baolin Guo, Shengxi Wu
Writing – original draft: Yangming Zhang, Yuqiao Xie, Zishuo Cheng, Yanran Zhang, Wenting Wang
Writing – review & editing: Baolin Guo, Shengxi Wu

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Availability of data
The supporting data can be obtained from the corresponding author upon reasonable request.

References
   https://doi.org/10.15585/mmwr.ss7011a1
   https://doi.org/10.1002/aur.2696
   https://doi.org/10.1002/aur.239
   https://doi.org/10.15585/mmwr.ss7010a1
   https://doi.org/10.1016/j.immuni.2021.09.014
   https://doi.org/10.1016/j.neuron.2020.11.007
   https://doi.org/10.1038/s41586-020-2777-8
   https://doi.org/10.1038/s41467-020-15530-3
   https://doi.org/10.1126/science.aav8130
   https://doi.org/10.1136/bmj.j6880
Microglia in autism spectrum disorder

https://doi.org/10.36922/an.v1i3.167


56. Needham BD, Tang W, Wu WL, 2018, Searching for the gut microbial contributing factors to social behavior in rodent...

https://doi.org/10.1002/dneu.22581


https://doi.org/10.1084/jem.20180794


https://doi.org/10.1016/j.molmed.2019.08.013


https://doi.org/10.9758/cpn.2018.16.3.246


https://doi.org/10.1152/ajpgi.00307.2021


https://doi.org/10.1016/j.pharmthera.2021.107989


https://doi.org/10.3390/molecules24183207


https://doi.org/10.3389/fimmu.2021.676255


https://doi.org/10.1371/journal.pone.0002906


https://doi.org/10.1126/science.aag3194


https://doi.org/10.1038/tp.2014.33


https://doi.org/10.3390/nu13041185


https://doi.org/10.1016/j.plefa.2018.04.003


https://doi.org/10.1016/j.euroence.2018.11.1106


https://doi.org/10.1016/j.mcn.2020.103493


https://doi.org/10.1002/aur.1571


https://doi.org/10.1016/j.biopsych.2016.08.024


https://doi.org/10.1177/088307389901400608


https://doi.org/10.1038/mp.2016.77


https://doi.org/10.1177/1362361315573636


https://doi.org/10.1126/science.aag3194


https://doi.org/10.1021/acschemneuro.6b00125