REVIEW

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The immune system and autism spectrum disorder: association and therapeutic challenges

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Autism spectrum disorder (ASD) is a neurodevelopmental disorder, affecting communication and behavior. Historically, ASD had been described as a purely psychiatric disorder with genetic factors playing the most critical role. Recently, a growing body of literature has been emphasizing the importance of environmental and immunological factors in its pathogenesis, with the autoimmune process attracting the most attention. This study provides a review of the autoimmune involvement in the pathogenesis of ASD. The microbiome, the representative of the innate immune system in the central nervous system (CNS), plays a critical role in triggering inflammation. Besides, a bidirectional communicational pathway between the CNS and the intestine called the gut-brain-axis is linked to the development of ASD. Moreover, the higher plasma level of pro-inflammatory cytokines in ASD patients and the higher prevalence of autoimmune disorders in the first-degree family members of affected persons are other clues of the immune system involvement in the pathogenesis of ASD. Furthermore, some anti-inflammatory drugs, including resveratrol and palmitoylethanolamide have shown promising effects by relieving the manifestations of ASD. Although considerable advances have been made in elucidating the role of autoimmunity in the ASD pathogenesis, further studies with stronger methodologies are needed to apply the knowledge to the definitive treatment of ASD.

Key words: autism spectrum disorder, autoimmune diseases, inflammation

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder, characterized by persistent impairment in social communication and restricted, repetitive, and stereotypical patterns of interests, behaviors, and activities (American Psychiatric Association, 2013). The word "spectrum" implies a range of heterogeneous symptoms with various severities and difficulty levels, providing a unique clinical definition for associated disorders (Paglia, 2020). According to the Diagnostic and Statistical Manual of Mental Disorders-V (DSM-V), the previously named mental disorders, including Asperger's disorder, autistic disorder, the pervasive developmental disorder not otherwise specified, and childhood disintegrative disorder, are now described under the umbrella term of ASD (American Psychiatric Association, 2013; Paglia, 2020).

Epidemiological studies have shown discrepancies in the estimation of the prevalence of ASD. For instance, the estimated prevalence for autistic disorder in 36 studies investigated by Fombonne (2005) ranged from 0.7 to 72.6 in 10,000. These variable estimates can be attributed to different factors, including inconsis-

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tent definitions of the disease and different reporting practices (Hansen et al., 2015). However, most studies proposed that the prevalence of ASD tends to increase over the past 50 years (Fombonne, 2005). In its updated guidelines in 2016, the United States' Center for Disease Control and Prevention reported the average incidence of ASD among US children aged eight years to be about 1.46% (Bjorklund et al., 2020). Besides, ASD has been reported to occur in all racial, ethnic, and socioeconomic groups (Baio, 2014). A meta-analysis study, conducted by Loomes et al. (2017) showed males are three times more susceptible to develop ASD, compared to females. These different prevalence rates can be explained by the fact that girls with ASD are less willing to receive the clinical diagnosis because of the possibility to mask social deficits in the female population, using a process called "camouflaging" (Volkmar et al., 2014; Loomes et al., 2017).

Although ASD has been extensively investigated during recent decades, etiological aspects of the disease have remained relatively unclear. Previous studies suggested that the interaction of genetic and environmental factors with the immune system could explain the condition (Gottfried et al., 2015). At the same time, researchers proposed some risk factors for ASD, including immunological abnormalities, advanced parental age, maternal treatment with some pharmaceutical drugs such as selective serotonin reuptake inhibitors (Matelski and Van de Water, 2016), preterm labor (Chung et al., 2020), male sex (Baio, 2014), and the presence of some inherited abnormalities like fragile X syndrome (Kaufmann et al., 2017). Among these risk factors, immunological factors have attracted so much attention so that a significant body of literature is forming, pointing to the role of the immune system as a possible etiology of ASD (Sciara et al., 2020). Furthermore, several immunological conditions, including gestational immune abnormalities, family history of autoimmunity, and coexistence of autoimmune diseases in individuals with ASD have been proposed to play a role in developing this disease (Edmiston et al., 2017). Anatomical studies revealed evidence of some brain structural changes related to neuroinflammation in patients with ASD. Epidemiological studies have also shown some evidence of simultaneously increased risk of ASD with the outbreak of atopic diseases in some societies (Liao et al., 2016; Sciara et al., 2020). Moreover, the presence of inflammatory cytokines in some patients with autism has demonstrated another clue of the immune system involvement in the pathological mechanism underlying ASD (Saghazadeh et al., 2019b). Accordingly, this paper aims to review the role of the immune system in the pathogenesis of ASD.

The interaction of the immune and nervous systems

The immune and nervous systems are among the most complicated body systems whose functions have some similarities. For example, both systems transport and receive messages *via* the secretion of transmitter molecules. They are also involved in storing data, creating the memory, and retrieving information (Habibi et al., 2009). Besides, both are capable of suppressing or strengthening their responses. The T/B regulatory cells in the immune system play a crucial role in suppressing immune responses for self-antigens (Sakaguchi et al., 2008; Rosser and Mauri, 2015). The inhibitory and excitatory subdivisions of neurons balance the neural system to function correctly (Yizhar et al., 2011).

The nervous system, divided into the central and peripheral systems, can influence the immune system either by straight innervation of immune organs or by secreting immune-modulatory hormones *via* the hypothalamic-pituitary-adrenal axis (Dunn, 2001; Nance and Sanders, 2007). The central nervous system (CNS), including the brain and the spinal cord, comprises neurons and glial cells. The glial cells in the mature CNS consist of oligodendrocytes, astrocytes, and microglia (Purves et al., 2001), each involved in secreting cytokines and triggering an immune response in the CNS. However, the microglial cells are the most prominent contributors in this regard (Bitzer-Quintero and González-Burgos, 2012).

The role of microglia in the pathogenesis of ASD

Microglial cells, characterized by their healing functions in local brain injuries (Streit, 1996), are macrophage-derived cells residing in the CNS. They are in charge of secreting different immune mediators, including pro-inflammatory and anti-inflammatory cytokines, prostanoids, chemokines, and thromboxane-A2 (Bitzer-Quintero and González-Burgos, 2012). Moreover, they have an essential role not only in the process of neurogenesis but also in neural death (Ketenmann et al., 2011). They are located in the brain parenchymal or perivascular regions and play a significant role in representing the innate immune system in these areas. When activated as antigen-presenting cells (APC), they trigger the secretion of T helper-1 (TH1)-derived cytokines, including IL-7 and tumor necrosis factor-alpha (TNF-alpha) (Bitzer-Quintero and González-Burgos, 2012). With the secretion of such immune mediators, the perivascular microglia signal and activate the parenchymal microglia,

which release different pro-inflammatory cytokines, resulting in CNS inflammation (Bitzer-Quintero and González-Burgos, 2012). Moreover, microglia affects the neurons in both embryonic and adult life, either indirectly *via* cytokines or by direct contact (Bilimoria and Stevens, 2015).

Recent studies have demonstrated that microglial functions are vital for brain development. They do this by taking the patterning and wiring processes of the developing CNS under control through programmed cell death, synaptic pruning, and synaptic maturation (Bilimoria and Stevens, 2015). Synaptic pruning is the process of the elimination of the extra non-required synapses in the development of the CNS. Several neurodevelopmental disorders, including socio-behavioral defects like ASD, have been linked to failure in this process (Kim et al., 2017). Furthermore, the C1q and C3, parts of the complement's cascade, are other contributors in the synaptic pruning process by their roles in assisting microglial functions. Therefore, impairment in these components can also be associated with neurological diseases (Stevens et al., 2007).

Role of astrocytes in the pathogenesis of ASD

Astrocytes are glial cells comprising the most extensive cell type in the brain (Freeman, 2010). Our knowledge of astrocytes was limited to mere their supporting role in CNS (Guillamón-Vivancos et al., 2015). Nevertheless, their active contribution in many CNS functions, including synapse formation, maturation, plasticity, and elimination, CNS development, construction of the BBB, neuronal plasticity, and blood flow regulation, have been discovered recently (Guillamón-Vivancos et al., 2015).

Astrocytes also play deciding roles in the pathophysiology of neurodevelopmental disorders such as ASD (Russo et al., 2018; Williams et al., 2014). Russo et al. (2018) demonstrated that astrocytes significantly impact synaptogenesis and neuronal morphological features in ASD using induced pluripotent stem cells (IPSCs). They were co-cultured in vitro with the normal neurons with ASD-derived astrocytes and showed morphological impairments in neurons and synaptogenesis defects (Russo et al., 2018). On the other hand, the co-culture of control-derived astrocytes with ASD-derived neurons improved ASD neuronal phenotypes and enhanced synapses revealed by higher synaptic puncta number (Russo et al., 2018). In this study, the ASD-derived neurons and the control neurons co-cultured with ASD-derived astrocytes were less complex. Furthermore, they had fewer branches than normal neurons, suggesting the pivotal role of astrocytes in ASD (Russo et al., 2018). Besides, the level of IL-6 was significantly higher in the ASD-derived astrocytes compared with control-derived astrocytes, and blocking IL-6 was associated with an enhancement in synaptogenesis. So it has been hypothesized that astrocyte-derived IL-6 may involve in the synaptic defect in ASD (Russo et al., 2018).

According to a post-mortal study, astrocytes are more abundant in the frontal cortex of autistic patients. Each has fewer branching processes, total branching length, and a smaller size than the astrocytes in the frontal cortex of control brains (Cao et al., 2012). Similar changes have been observed in neuroligin-3 knockdown mice used as an animal model for ASD (Cao et al., 2012). Moreover, the Wnt/β-catenin pathway, known to be involved in astrocyte development regulation, significantly decreased in autistic brains (Cao et al., 2012).

The interaction between glial cells and neurons in ASD

Synapses are specific structures enabling a neuron to pass electrical or chemical signals to another neuron (Blanco-Suárez et al., 2017). Astrocytes in the CNS are closely associated with many synapses *via* their specialized processes called perisynaptic astrocytes' processes (PAPs) (Blanco-Suárez et al., 2017). The combination of PAPs and pre-and post-synaptic structures forms a concept named the "tripartite synapse" (Araque et al., 1999). In the developing brain, astrocytes regulate synapse formation *via* secreting varied factors, including thrombospondin, hevin, glypicans, brain-derived neurotrophic factor (BDNF), secreted protein acidic and rich in cysteine (SPARC), and TNF-a (Allen, 2014). These factors mainly induce glutamatergic synapse formation. Although not all astrocyte-derived factors lead to synapse formation, SPARC inhibits its synapse formation (Kucukdereli et al., 2011). The astrocyte gliotransmitters – like ATP, adenosine, and D-serine – can act on pre-or post-synaptic compartments to strengthen or weaken neuronal transmission and plasticity (Chung et al., 2015). For example, trospondin inhibits presynaptic release at glutamatergic synapses (Chung et al., 2015). Excessive glutamate in synapses leads to damage and destruction of the synapse. Accordingly, astrocytes uptake the excessive glutamate in synaptic cleft *via* glutamate transporter 1 (GLT-1) and glutamate aspartate transporter (GLAST). The absorbed glutamate is then converted to glutamine in astrocytes and recycled to neurons for maintaining synaptic transmission (Blanco-Suárez et al., 2017). Furthermore, astrocytes have an active role in

buffering extracellular K(+) to support neuronal networks by rectifying potassium KIR4.1 channels (Chever et al., 2010). Given synapse abnormalities are major characteristics of neurodevelopmental disorders like ASD (Blanco-Suárez et al., 2017), changing astrocyte functions presents a novel target to improve the disease manifestations.

On the other hand, microglia and astrocytes interact with each other by secreting various cytokines and signaling molecules. For example, reactive microglia activate and proliferate astrocytes by secreting many cytokines, including IL-1, IL-2, IL-6, TNF-a, and IFN-y (Matta et al., 2019). On the other hand, activated astrocytes discharge ATP to maintain microglial activity (Matta et al., 2019). Although these states of activity play beneficial roles in CNS injuries, the prolonged activation of these two glia can promote neuroinflammation and lead to disorders like ASD. Taken together, the extent to which the neurons and glial cells interact with each other is a crucial element for understanding the pathological mechanisms underlying various neurological diseases and leads to a better perception of the interaction of immune and nervous systems.

The innate immune system and ASD

The innate immune system is a significant contributor to the pathogenesis of autism. While this system defends the body against external pathogens, innate immunity plays a role in developing ASD by triggering inflammation in the CNS (Salam et al., 2018). Two major arms impacting the development of ASD are microglia/astrocyte and gut-brain-axis, which will be further dissected.

Microglia/astrocyte

As mentioned above, microglia and astrocytes are known as essential contributors to the pathogenesis of neurodevelopmental disorders, including ASD.

Microglia represents CNS-resident macrophages originating from the yolk sack (Gomez Perdiguero et al., 2015). They can experience different phenotypes, namely M1 and M2, to respond to different molecular and environmental stimuli and signals (Orihuela et al., 2016). Either classic or alternative way can trigger their activation. Bacterial products like lipopolysaccharide, Th1 cytokines such as IFN-Y and TNF-a, and pathogen-associated molecular patterns stimulate the classic way of activation and produce M1 phenotype (Gordon and Mantovani, 2011; Orihuela et al., 2016). M1 microglia are inflammatory cells, which secrete pro-inflammatory cytokines (such as TNF-α, IL-1α, IL-1β, and IL-6) and act as microbicidal antitumorigenic agents (Zhang et al., 2016).

Moreover, these cytokines can further maintain the polarization of microglia into the M1 phenotype (Cherry et al., 2014). IL-4/IL-13 induces alternative activation and leads to M2-polarized microglia, which show anti-inflammatory features having roles in tissue repair and inflammation resolution (Orihuela et al., 2016). Depending on what cytokine stimulates the microglia activation, M2 microglia are divided into several subgroups, including M2a, M2b, and M2c. The main role of M2a is the suppression of inflammation (Cherry et al., 2014), while M2c has roles in tissue remodeling and matrix deposition (Mantovani et al., 2004), and M2b, which are less understood, can activate Th2 response and play a potential role in the initiation of M2 response (Cherry et al., 2014). Although these subgroups function somewhat differently, the common property of all of them is the production of mediators and receptors with the capacity to inhibit inflammation (Cherry et al., 2014). M1 and M2 microglia are distinguishable *via* arginase1+ staining (Mills, 2012).

Microglial phenotype switching is a critical concept leading to homeostasis in the CNS.

For example, in acute conditions such as traumatic brain injuries or release of DAMPs (damage-associated molecular patterns) following infections or ischemic reperfusion injury, the M1 microglia, part of the innate immune system, are activated, and secrete pro-inflammatory cytokines and reactive oxygen synthesis (ROS), leading to the elimination of invading agents and removing dead cells (Cherry et al., 2014). This inflammatory response is not only harmful, but also it is an important step in brain homeostasis (Lucas et al., 2010). The inflammatory response then shifts to the anti-inflammatory response, in which M2 microglia are responsible for clearing debris, angiogenesis, and extracellular matrix deposition and play a significant role in neuroprotection. When the pro-inflammatory response does not yield, the persistent presence and production of inflammatory cytokines and reactive oxygen species by M1 macrophages can lead to cell death and further tissue damages, including synapse changes. Furthermore, the inactivation of the M2 microglial response can also result in a prolonged state of inflammation in the CNS (Lucas et al., 2010). These conditions are associated with chronic inflammation in the CNS. Therefore, the failure in microglial phenotype switching is a potential contributor to neurodevelopmental disorders like ASD.

In a study conducted by Vargas et al. (2005) significant signs of microglial activation have been shown in different regions of post mortem brains in autistic patients, including the cortex, white matter, and

cerebellum, compared to brains of the members of the control group who had not any neurological disorders (Matta, et al., 2019). In this study, the signs of increased astrocyte activity in all areas, as mentioned earlier, marked by glial fibrillary acidic protein expression, have also been detected (Matta et al., 2019). These changes were most prominent in the cerebellum tissue (Matta et al., 2019).

According to another study, the density of microglia in the dorsolateral prefrontal sections of the brain cortex of autistic patients was significantly increased (Morgan et al., 2010). Another consistent study investigating the brain autopsies of individuals with autism found a marked increased microglial density in the fronto-insular (FI) and the visual cortex (VC) regions compared to neuro-normal individuals. Given that these two brain regions are entirely separate from each other, the authors of this study have suggested a generalized increase in microglial activity in the whole brain cortex of ASD patients (Tetreault et al., 2012). The difference in the autistic brain is not only confined to the quantity of microglia, but also the morphological parameters in microglia vary. For instance, despite a similar number of microglia in the brain amygdala in patients with ASD, the resident microglia in the amygdala were morphologically different compared to neuro-normal individuals (Morgan et al., 2014). Another study also demonstrated a significant elevation in the primed type of microglia and a remarkable decrease in the ramified type of microglia in the postmortem brains of patients with ASD compared to normal developing individuals despite the similar total density of the microglia (Lee et al., 2017).

One of the possible triggers of microglial activation in patients with ASD is the increased secretion of extracellular vesicles (EV) in these patients (Tsilioni and Theoharides, 2018). EVs, secreted from different cells, alter the function of target cells. In patients with ASD, they trigger microglial cells to secrete a higher amount of pro-inflammatory cytokines like IL1-B, a process that can ultimately lead to ASD development (Tsilioni and Theoharides, 2018).

The microbiome and gut-brain axis

The symptoms of gastrointestinal (GI) disturbances are relatively common among patients with ASD (Yang et al., 2018). One of the leading causes of these symptoms is intestinal microbiota imbalance, a condition called dysbiosis (Nitschke et al., 2020). The intestinal microbiota plays a vital role in the function and development of CNS, neuroendocrine, and neuroimmune systems (Nitschke et al., 2020). The gut-brain axis (GBA) is a bidirectional pathway between the CNS, autonomic nervous system (ANS), the hypothalamic-pituitary-adrenal axis (HPA), and the enteric nervous system, enabling direct and indirect communication among them (Ferguson and Solo-Gabriele, 2016; Sivamaruthi et al., 2020). The sympathetic and parasympathetic nerves mediate efferent signals from the CNS to the intestine, regulating microbiome composition and transferring afferent signals from the intestine to the CNS (Sivamaruthi et al., 2020).

Besides, the microbiome transfers different messages *via* either secreting various neuro-active molecules such as acetylcholine or *via* activating the vagus nerve directly (Petra et al., 2015). Following environmental stresses and pro-inflammatory cytokine release caused by the change in the intestinal flora's composition, the HPA, responsible for emotional responses and memory, is activated, which ultimately results in cortisol secretion. Cortisol is capable of altering the brain, the intestinal endothelium, and the gut microbiota composition. Hence, the intestinal effector cells such as endothelium and immune cells are under CNS control by the hormonal and neuronal pathways. Besides, any dysregulation in the intestinal effector cells may lead to microbial composition and dysbiosis changes. This process can be followed by CNS development abnormalities and dysfunctions, including behavioral and neuropsychiatric diseases (Sivamaruthi et al., 2020). Moreover, a study conducted by Eltokhi et al. (2020), demonstrated that the microbiome has a critical role in the synaptic pruning process, specifically in the prenatal and early postnatal periods of life.

While discrepancies exist upon which bacteria are most responsible for dysbiosis, recently, the bacteria "Clostridium difficile" has been found to be significantly increased in the stool exam of individuals with ASD compared with normal controls (Saurman et al., 2020). Another study also revealed that the investigated autistic children with GI abnormalities had significantly higher levels of the intestinal bacteria "Clostridium perfringens" than neuro-normal children without GI symptoms (Finegold et al., 2017). However, no significant microbiota differences were found between autistic children and normal controls (Gondalia et al., 2012). These inconsistencies may be justified by the small sample sizes surveyed in these studies. The elucidation of the role of intestinal microbiome in patients with ASD can lead to better future interventions for relieving behavioral and cognitive autistic symptoms, including fecal microbiota transplantation, change in the diet, and utilization of probiotics and prebiotics (Eltokhi et al., 2020). For instance, dietary polyphenols were found to have promising effects on the manifestations of ASD by impacting the GBA (Serra et al., 2020).

Inflammatory and anti-inflammatory cytokines in individuals with ASD

Altered levels of cytokines are known as an essential component of immune dysregulation in patients with ASD. In a case-control study, the expression of the genes of IL-6, an inflammatory protein, and heat shock protein 70i (HSP70i), a stress-related protein, were significantly higher in children with ASD. Furthermore, the plasma levels of Prx2 and Prx5 (peroxiredoxins), antioxidant enzymes responsible for protecting the brain against oxidative stress, were significantly higher in children with ASD compared to typically developing children; signifying neuroinflammation as a part of autism pathogenesis (Abruzzo et al., 2019). Moreover, it has been reported that the granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon-*gamma* (IFN-γ), IL-6, IL-9, IL-22, T-bet, and phospho-signal transducer and activator of transcription-3 (pSTAT3) producing CD45 cells have been remarkably increased in the children with ASD compared with control subgroup (Ahmad et al., 2020).

It has also been shown that patients with ASD have decreased anti-inflammatory response of T helper-2 and the increased pro-inflammatory response of T helper-1 cells (Bjorklund et al., 2016).

In contrast to the mentioned studies, which demonstrated higher levels of inflammatory cytokines in patients with ASD, in a case-control study conducted by Gomez-Fernandez et al. (2018) no significant differences were observed in the levels of cytokines between the children with ASD and normal developing children, except for the nerve growth factor (NGF) which was higher in the autistic children. However, this study has shown lower plasma levels of neural cell adhesion molecule (NCAM) and higher NGF levels in ASD patients without developmental regression compared with the subgroup with developmental regression. This highlights the difference in pathological pathways among various subgroups of ASD (Gomez-Fernandez et al., 2018).

Moreover, in a meta-analysis, higher plasma levels of pro-inflammatory cytokines, including IFN-γ, IL-1β, IL-6, and TNF-α were reported in patients with ASD compared to typically developing individuals (Saghazadeh et al., 2019b). Furthermore, significantly higher TNF-α and S100B (a calcium-binding protein) in autistic patients have been demonstrated in another study. Besides, the S100B peripheral level was higher in patients with severe ASD compared to those with mild to moderate forms. However, other pro-inflammatory cytokines were similar between the subjects with ASD and the ordinary individuals (Guloksuz et al., 2017).

One study addressed cytokine profiles in the siblings of ASD patients, including autistic children (N=80), unaffected siblings of the autistic children (51 persons), and unrelated normal controls (N=86). An increased plasma level of IL-6 was found in both autistic children and their siblings compared to the unrelated healthy control group. On the other hand, TNF-α and IL-8 were exclusively elevated in autistic children. However, the IL-9 and IL-10 levels did not show any differences between the mentioned three groups (Alzghoul et al., 2019).

The results of a meta-analysis showed that ASD patients have higher serum levels of IL-8 (Masi et al., 2015). Furthermore, IL-8 was the only cytokine that showed higher levels after adjusting parental cytokines in children with ASD, making IL-8 a promising biomarker for diagnosing ASD and contributing to the pathogenesis (Shen et al., 2020). In contrast, another study reported lower serum levels of IL-8, but higher brain levels were reported in patients with ASD (Businaro et al., 2016).

Besides, increased activity of superoxide dismutase (SOD) in the neutrophils and monocytes was found in patients with ASD compared to normal developing individuals. In comparison, the activities of glutathione peroxidase and glutathione reductase were reduced or unaltered in this population. This highlights the possible role of the dysregulated enzymatic antioxidant network in the pathogenesis of autism (Nadeem et al., 2019). On the other hand, a moderate reduction in the serum IL-10 levels, a little decreased serum IL-1 receptor antagonist, and a slightly increased plasma IL-5 level were found in patients with ASD (Saghazadeh et al., 2019a).

Although ASD has a strong genetic component, exposure to some environmental factors during pregnancy has been associated with offspring's autism-like behaviors. Valproic acid (VPA) is an anti-epileptic drug widely used in pregnancy (Zhao et al., 2019). The prenatal exposure to VPA in rodents has been associated with behavioral deficits consistent with ASD. This association was also approved in non-human primates in 2019 (Zhao et al., 2019). The VPA-induced animal model of autism was developed in 1996, and since then, this model has been extensively used to investigate different molecular pathways in ASD (Rodier et al., 1996). In an animal study, rats were intraperitoneally (IP) injected with VPA on day 12.5 of gestation, and then their inflammatory profile was investigated at 11 and 13 weeks of age. The VPA-induced rats showed significantly increased expression of pro-inflammatory cytokines – including IL-1B and TNF-a – and reduced expression of social behavior-related genes like BDNF and neuroligin-3 in the hippocampus compared

to control rats. Besides, the hippocampal expression of gamma-aminobutyric acid (GABA) and glutamic acid decarboxylase (GAD) was decreased (Win-Shwe et al., 2018). On the other hand, maternal immune activation in pregnancy-induced by polyinosinic-polycytidylic acid (poly (I:C)) is associated with autism in offspring (Lammert and Lukens, 2019). Poly (I:C) exposure in pregnancy has been associated with elevated immune response in several animal studies (Haddad, Patel, et al., Schmid, 2020). However, in a recent study on rats, the IP injection of poly (I:C) on gestational day 15 resulted in increased IL-6 level 6 h and 24 h post-injection but not in postnatal days (Murray et al., 2019). Lipopolysaccharide (LPS) administration in mice has also been connected to autism-like behaviors, and CNS changes consistent with autism (Custódio et al., 2018). In a study, Swiss mice were neonatally challenged with LPS in postnatal days (PN) 5-7 and analyzed in PN35 and PN70. The mice showed increased levels of IL-4 in the prefrontal cortex (PFC), hippocampus (HC), and hypothalamus (HT) and decreased levels of IL-6 in PFC, HC, and HT. Moreover, the BDNF levels were increased in both PN70 male and female mice. LPS-induced male mice showed increased myeloperoxidase (MPO) activity in both PN35 and PN70. At the same time elevated levels of IFNγ and nitrite and decreased parvalbumin were observed in PN70 male mice (Custódio et al., 2018). These observations have suggested a sex and age-specific alteration in cytokine profile resembling ASD following LPS-administration (Custódio et al., 2018).

Taken together, the available data on the profile of pro-inflammatory cytokines mainly indicated increased serum levels of IFN-γ, IL-1β, IL-6, and TNF-α in patients with ASD. However, further investigations on the pro-inflammatory and anti-inflammatory cytokines in autistic patients with adequate sample sizes are recommended.

The family history of immune dysregulation in children with ASD

Concerning the possible involvement of autoimmunity in the pathogenesis of ASD and the inheritable nature of most autoimmune disorders, several studies have investigated autoimmune diseases in the family members of autistic children. A multi-site case-control study investigated the presence of asthma, any autoimmune diseases, and allergies in the family members of autistic children. The mothers with a past medical history of asthma were significantly more likely to have a child with autism than the mothers ascertained from the general population (*OR*=1.26, *P*=0.05). Besides, the prevalence of other autoimmune disorders and allergies was higher in autistic children's mothers, although the differences were not significant. Moreover, this study reported that maternal immune conditions in pregnancy are significantly followed by developmental disorders in the child (*OR*=1.37, *P*=0.03) but not autism alone (*OR*=1.29, *P*=0.15). However, no significant association was found between paternal autoimmune diseases and the development of autism in children (Croen et al., 2019).

In a cohort study, a significant association was found between infantile autism and family history of type 1 diabetes mellitus (T1DM). Besides, a significant association was reported between maternal history of rheumatoid arthritis (RA) and celiac disease and the presence of ASD in the children (Atladóttir et al., 2009). Moreover, this study showed that the association between the family history of RA and ASD in the child was limited to maternal history, compared with an older study that showed a higher prevalence of ASD in children with an overall family history of RA (Comi et al., 1999). These conflicting results may emphasize an altered antibody exposure in the prenatal period in children with ASD (Atladóttir et al., 2009).

To shed light on the specific factor leading to ASD in children and immune dysregulation in their family members, Mostafa and Shehab (2010) designed a study and proposed that the complement 4B null allele has a significant role in ASD. They demonstrated that C4B null allele was significantly more frequent in children with ASD compared to the control group (*P*<0.001) and also had a significant association with both ASD (*OR*=6.26, 95% *CI*=2.5-14.1) in the children and their family history of autoimmunity (*OR*=21, 95% *CI*=2.5-14.1). Besides, the family history of autoimmune abnormalities in children with ASD was significantly more frequent than the standard developing control group (*P*<0.001) (Mostafa and Shehab, 2010).

Furthermore, regressive autism, which is defined as the loss of speech and social skills several months after birth, was associated with a family history of autoimmune diseases (*OR*=1.89) (Molloy et al., 2006). The authors also found that autoimmune thyroid disease was the only autoimmune disorder in family members of autistic children to have a significant association with the regressive type of ASD in the child (*OR*=2.09, *P*=0.003). It was also shown that children with more than one family member affected with autoimmune diseases were more likely to be diagnosed with regressive ASD rather than non-regressive type (*OR*=1.89, *P*=0.009) (Molloy et al., 2006). Besides, maternal hypothyroidism diagnosed and treated for the first time after the child's birth was significantly associated with the presence of autism in offsprings. The abnormal

level of thyroid hormones in mothers with untreated hypothyroid during pregnancy may result in neurodevelopmental disorders in the child, including ASD (Brown et al., 2015).

Besides, according to an animal study, extreme maternal hypothyroxinemia was associated with a four times greater probability of having a child with autism (adjusted *OR*=3.89, *P*<0.001) (Román, 2013). However, another study reported that maternal autoimmune diseases were significantly associated with developmental disorders in their offsprings (*OR*=1.46) but not exclusively with autism (Lyall et al., 2014). Moreover, another study reported a higher frequency of maternal immunological abnormalities in 4 years around pregnancy. However, it did not vary significantly between the autistic children and the control group (10.3% *vs.* 8.2%, *P*=0.15), except for maternal psoriasis, which was significantly associated with developing ASD (p=0.003, OR=2.7) (Croen et al., 2005). Furthermore, according to Mouridsen et al. (2007) infantile autism (IA) was significantly associated with maternal ulcerative colitis (*P*=0.05) and paternal T1DM (*P*=0.02). However, they found no differences in the prevalence of autoimmune diseases between mothers of autistic children and mothers recruited from the general population (*P*=0.71). The prevalence of autoimmune diseases in fathers in the case and control group was 8.6% *versus* 4.6%, respectively (*P*=0.14). Besides, Sweeten et al. (2003) showed that the frequency of autoimmune abnormalities was significantly higher in the family members of children with pervasive developmental disorders, a term used to describe developmental disorders, including autism in the DSM-IV definition. Despite some discrepancies, some autoimmune disorders in the family such as T1DM, hypothyroidism, RA, psoriasis, and ulcerative colitis are associated with the development of ASD in children. However, there is still a need for more research in this field.

Known concomitant autoimmune diseases in patients with ASD

Up to the present, the co-occurrence of some autoimmune disorders, including T1DM, hypothyroidism, celiac disease, and inflammatory bowel disease with ASD, has been investigated. The prevalence of ASD among children with T1DM who attended a diabetic clinic in Toronto was greater than the general population (Freeman et al., 2005). In line with this study, it has been clarified that the prevalence of ASD in T1DM patients in Colorado and Ontario were 1.16% and 0.9%, respectively, both higher than the ASD prevalence in the normal population living in Colorado (0.7%) (Stanek et al., 2019). The same authors found a lower HbA1c level (*P*<0.0001) and insulin pump (*P*<0.0001) in ASD+T1DM patients compared to T1DM patients. However, several studies examined a higher prevalence of T1DM in ASD patients, including a survey among children with pre-diagnosed T1DM (N=10032), which indicated no difference in the prevalence of ASD between these children and normal children. They have also reported lower HbA1c concentrations and lower pump use in children with ASD, which may be due to the more regimented routines in this population (Bethin et al., 2019). Moreover, no higher prevalence of ASD was found in children with T1DM (N=5178) in Finland (Harjutsalo and Tuomilehto, 2006).

Besides, no connection has been found between the overall ASD prevalence and the increased blood levels of TSH as a sign of hypothyroidism in the early life period. However, it has been suggested that the high TSH level may have an association with the regressive sub-phenotype of ASD (Ames et al., 2020).

Although case reports have shown celiac disease and ASD's co-occurrence, other studies did not support this finding (Ludvigsson et al., 2013; Bavykina et al., 2018). The predominant gluten sensitivity was reported in 41.9% of ASD children; however, no beneficiary role of a gluten-free diet was found in children with ASD (Buie, 2013). Other studies which reported no relationship between ASD and celiac disease were conducted on small sample sizes (Juneja et al., 2018; Batista et al., 2012; Pavone et al., 1997). In a registry in Sweden, patients with celiac disease (27000) showed no association between prior ASD and celiac disease. An apparent increased risk of ASD was also reported in patients with normal mucosa but with positive celiac auto-antibodies (*OR*=4.57; 95% *CI*=1.58-13.22) (Ludvigsson et al., 2013).

As pointed out in the previous sections, ASD pathogenesis may be associated with microbiome dysregulation and the presence of inflammation in the bowels. In line with this, a retrospective case-cohort study indicated that children with ASD had a higher prevalence of Crohn's disease and ulcerative colitis than the control group (Lee et al., 2018).

Anti-inflammatory treatment in relieving the symptoms of ASD

As mentioned earlier, there is recently growing literature pointing out the critical role of inflammation in the pathogenesis of autism. Accordingly, anti-inflammation therapies have much been investigated for relieving autism manifestations. Some anti-in-

flammatory interventions, which have been studied in patients with autism, are sulforaphane, osthole, fexofenadine, resveratrol, palmitoylethanolamide (PEA), pioglitazone, acetylcysteine, propentofylline, L-carnosine, yokukansan, spironolactone, celecoxib, flavonoid luteolin, corticosteroids, minocycline, and stem cell therapy.

Sulforaphane is found chiefly in cruciferous vegetables like broccoli, sulforaphane is known for its anti-inflammatory and antioxidant effects (Durham et al., 2014). In a placebo-controlled randomized trial among men aged 13 to 27 years with ASD (N=44), sulforaphane significantly improved autistic behaviors compared with the placebo group. In other words, it led to a substantial decrease in the scores of the Aberrant Behavior Checklist ($p<0.001$), social responsiveness scale ($p<0.017$), and clinical global impression improvement scale ($P=0.007$-0.015) (Singh et al., 2014).

Osthole is used in Chinese traditional medicine and has been reported to have anti-inflammatory effects (Zhang et al., 2015). Similarly, fexofenadine is a known anti-histamine drug with anti-inflammatory effects (Kordulewska et al., 2019). According to Kordulewska et al. (2019) the cyclooxygenase 2 (COX-2) pathways may have a role in the pathogenesis of autism, and osthole or fexofenadine application in children with autism can decline the COX-2 inflammatory effects. It may lead to a reduction in autism development.

Resveratrol (RSV) is a polyphenolic substance, which can be obtained from some plants and fruits and recently has been extensively the subject of research for its numerous beneficial effects, including antioxidant and anti-inflammatory effects (Gambini et al., 2015). Resveratrol acts by affecting apoptosis of activated T cells and suppressing TNF-α, IL-17, and the other pro-inflammatory cytokines (Diaz-Gerevini et al., 2016). An animal study showed resveratrol has promising effects on restoring all the core and associated manifestations of autism by inhibiting oxidative-nitrosative stress in the rats (Bhandari and Kuhad, 2017). Moreover, resveratrol improved defective mitochondrial fatty acid oxidation in patients with autism (Barone et al., 2019). However, no randomized control trial has been conducted up to date on resveratrol effects on patients with ASD.

Palmitoylethanolamide, an endocannabinoid molecule, has potential anti-inflammatory effects (Khalaj et al., 2018). It significantly improved autism-related irritability and hyperactivity symptoms when adjunct to risperidone therapy (Khalaj et al., 2018). Consistently, it improved autistic-like behaviors by affecting intestinal microbial composition in mice (Cristiano et al., 2018).

Pioglitazone is a member of thiazolidinedione drugs, widely used as an anti-diabetic agent with anti-inflammatory effects. Daily therapy with 30-60 mg of pioglitazone in children with autism (N=30) has led to apparent clinical improvements in irritability, lethargy, stereotypy, and hyperactivity subscales of autism (Boris et al., 2007). Moreover, in an animal study, daily pioglitazone use in rats, which were induced by lipopolysaccharide in the prenatal period, improved their autistic-like behaviors and abolished their IL-6 levels (Kirsten et al., 2018).

Acetylcysteine is known for its antioxidant effects and has recently-demonstrated anti-inflammatory properties (Uraz et al., 2013). Acetylcysteine could reduce the aggressive and unpredictable behaviors in a 17-year-old boy who has autism, who did not respond to the other medications (Stutzman and Dopheide, 2015).

L-carnosine belongs to the family of hybrid peptides with reported anti-inflammatory and anti-oxidation effects (Tsai et al., 2010). In a randomized, double-blind placebo-controlled study, children with autism (N=70) were enrolled and randomly assigned to 10-week therapy with placebo plus risperidone or L-carnosine plus risperidone regimen. L-carnosine subgroup had better scores in the hyperactivity-non-compliance subscale of the Aberrant Behavior Checklist-Community rating scale (Hajizadeh-Zaker et al., 2018). However, this study reported no significant differences in the irritability subscale between groups (Hajizadeh-Zaker et al., 2018).

Spironolactone is a potassium-sparing diuretic, which has anti-androgenic effects (Marchezan et al., 2018). It has also shown its potential to be used as an anti-inflammatory drug by inhibiting the production of inflammatory cytokines such as TNF-α (Bendtzen et al., 2003). A case-report study found that spironolactone had promising effects on autistic behaviors and ABC scores of a 12-year-old autistic boy (Bradstreet et al., 2007).

Flavonoid luteolin can be found in plenty of plants. It has been demonstrated that it can inhibit the secretion of pro-inflammatory cytokines from mast cells in humans (Kempuraj et al., 2005). In an uncontrolled case series, the use of luteolin for at least four months by children with autism (N=37) improved GI and allergy symptoms in 75%, attention and eye contact in 50%, and social interaction in 25% of them (Theoharides et al., 2012). In line with this study, an open-label trial reported the beneficiary roles of combined flavonoid luteolin and quercetin in relieving autism symptoms (Taliou et al., 2013). Moreover, a significant improvement was reported in autistic behaviors in one mouse model following the combined administration of luteolin and palmitoylethanolamide (Bertolino et al., 2017).

Table 1. Anti-inflammatory therapies among subjects with ASD.

Therapy	Methodology	Measure	Sample size	Dosage	Period	Outcomes	References
Sulforaphane	Placebo-controlled, double-blind, randomized trial	ABC[1]-SRS[2]-CGI-I[3]	29	50–150 μmol	18 weeks	Decline in scores: 34% for ABC, 17% for SRS n CGI-I: SI, VC and AB improvements	(Singh et al., 2014)
(Palmitoylethanolamide (PEA) + risperidone) *versus* (risperidone + placebo)	Randomized, parallel-group, double-blind placebo-controlled trial	ABC-C[4]	70	600 mg PEA twice daily	10 weeks	Significant improvements in ABC-irritability and hyperactivity/ noncompliance symptoms (p=0.001), great effect on inappropriate speech (p=0.051)	(Khalaj et al., 2018)
L-carnosine add on to risperidone	Randomized, double-blind, placebo-controlled trial	ABC-C - SORS	70	800 mg/day l-carnosine in 2 divided doses	10 weeks	Significant improvement in hyperactivity/ noncompliance subscale (p=0.044)	(Hajizadeh-Zaker et al., 2018)
Minocycline as an adjunctive to risperidone	Randomized controlled trial	ABC-C	46	50 mg twice per day	10 weeks	Significant improvement in irritability, hyperactivity/ noncompliance	(Ghaleiha et al., 2016)
Celecoxib as an adjunctive to risperidone	Randomized double-blind placebo-controlled	ABC-C	40	300 mg/day	100 weeks	Significant improvement in Irritability, Lethargy/Social Withdrawal and Stereotypic Behavior	(Asadabadi et al., 2013)
Flavonoid luteolin + flavonoid quercetin	Prospective, open-label trial	VABS[5]-ABC - CGI-I - Autism Treatment Evaluation Checklist	50	1 capsule (100 mg luteolin, 70 mg quercetin) per 10 kg weight per day	26 weeks	Reduction (26.6%-34.8%) in Aberrant Behavior Checklist subscale scores- significant improvement in adaptive functioning measured by VABS- Transient increased irritability (1-8w) in 27 subjects	(Taliou et al., 2013)
Pioglitazone	Small cohort	ABC	25	30 mg (age 3-5) or 60 mg (age 6-17) daily	3-4 months	Significant improvement in irritability, lethargy, stereotypy, and hyperactivity	(Boris et al., 2007)
Flavonoid luteolin + flavonoid quercetin	Uncontrolled open case series	Observations of the responses by the parents of children with ASD	37	2 capsules/ 20 kg weight or at least 400 mg total flavonoid	at least 4 months	75% improvement in GI and allergy symptoms, 50% in eye contact and attention, 25% in social interaction, 10% in a resumption of speech	(Theoharides et al., 2012)
Acetylcysteine	Case report	Occupational and recreation therapists observations	1	600 mg twice daily	6 weeks	Reduction in the patient's aggressive behavior, tantrums, and irritability	(Stutzman and Dopheide, 2015)

Therapy	Methodology	Measure	Sample size	Dosage	Period	Outcomes	References
Spironolactone	Case report	ABC	1	2 mg/kg daily	4 weeks	79% improvement in irritability, 83% decrease in lethargy, a 60% reduction of stereotypy, 72% reduction of hyperactivity, and a 67% decrease in inappropriate speech	(Bendtzen et al., 2003)
Corticosteroids	Case report	Observation and WISC-R[6]	1	Begin with 2 mg/kg prednisolone, titrated monthly by 0.5 mg/kg from weeks 4 through 12	28 weeks	Amelioration of language abilities and behavior and increase in IQ, increase in spontaneous speech, greater responsiveness to verbal communications, and improved social relatedness	(Stefanatos et al., 1995)
Resveratrol	Animal study	–	–	5, 10 and 15 mg/kg	4 weeks	Restore all the neurological, sensory, behavioral, biochemical and molecular deficits in autistic rats	(Bhandari and Kuhad, 2017)
Palmitoylethanolamide (PEA)	Animal study	Serum parameters, mitochondrial parameters, Self-Grooming test, Marble burying assay	–	10 or 30 mg/kg	10 days	Improvement in autistic-like behaviors in mouses, mitochondrial dysfunction, reduction in the overall inflammatory state and expression of pro-inflammatory cytokines	(Cristiano et al., 2018)
Pioglitazone	Animal study	Plasma evaluation, play behavior evaluation, vocalization evaluation	6-8 rats	0.25 mg/kg/day	10 days	Reduction in IL-6 level, improvement in social interaction and the number of vocalizations	(Kirsten et al., 2018)

1 Aberrant Behavior Checklist.
2 Social Responsiveness Scale.
3 Clinical Global Impression – Improvement scale.
4 Aberrant behavior checklist – community.
5 Vineland Adaptive Behavior Scales.
6 Wechsler Intelligence Scale for Children-Revised.

Corticosteroids are a well-known group of anti-inflammatory drugs, widely used to treat plenty of disorders. A case report showed improved language abilities and autistic behaviors in a 6-year-old child with a pervasive developmental disorder (by the definition of DSM-IV) (Stefanatos et al., 1995). Furthermore, two childhood disintegrative disorder cases showed a significant improvement in behavior, motor regression, and language following corticosteroid therapy (Mordekar et al., 2009).

Minocycline is an antibiotic whose neuroprotective and anti-inflammatory effects have been explored recently (Elewa et al., 2006). In a randomized control trial conducted by Ghaleliha et al. (2016) forty-six children with ASD were recruited and entered in 10-week risperidone plus minocycline or risperidone plus placebo

treatment groups. The children receiving minocycline as an adjunctive therapy had better scores in ABC-C irritability (P=0.02) and hyperactivity/noncompliance (P=0.002) sub-scales. However, there were no significant differences in terms of social withdrawal, stereotypical behaviors, and inappropriate speech sub-scales of ASD between minocycline and placebo groups (Ghaleiha et al., 2016).

Celecoxib is a non-steroidal anti-inflammatory drug (Shin, 2018). Celecoxib was investigated in a 10-week randomized control trial among children with ASD (N=40). They entered either risperidone plus celecoxib or risperidone plus placebo treatment groups. The results indicated that children who received a celecoxib-added regimen had significant improvement in the subscales of irritability (P<0.001), lethargy/social withdrawal (P<0.001), and stereotypic behaviors (P<0.001) compared with the placebo group. Moreover, the rate of adverse effects was similar between the two groups (Asadabadi et al., 2013).

Stem cell therapy alleviates the symptoms of autism by an unknown molecular pathway. One explanation for its effects is the paracrine activity by stem cells, by which plenty of anti-inflammatory cytokines, including exosomes are secreted (Alessio et al., 2020).

CONCLUSION

Taken together, autoimmunity may be an essential nominee for the pathogenesis of ASD. The involvement of microglia and astrocytes in the process of CNS inflammation, the role of the gut-brain axis in the CNS development, the presence of higher pro-inflammatory cytokines in patients with ASD, the higher prevalence of immune dysregulation in the family members of affected children, and the successful application of some anti-inflammatory therapies in patients with ASD are some pieces of evidence to count ASD as a neuroimmune disorder. However, inconsistencies exist, and there are still many unanswered questions. Thus, further studies with robust methodologies should be a priority.

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