Immunological Disturbance in Autism Spectrum Disorders

Subjects: Pathology

Contributor: Maria de los Angeles Robinson-Agramonte , Elena Noris García , Jarasca Fraga Guerra , Yamilé Vega Hurtado , Nicola Antonucci , Neomar Semprún-Hernández , Stephen Schultz , Dario Siniscalco

Autism spectrum disorder (ASD) is a group of complex multifactorial neurodevelopmental disorders characterized by a wide and variable set of neuropsychiatric symptoms, including deficits in social communication, narrow and restricted interests, and repetitive behavior. The immune system consists of a set of molecules and cells that are organized in tissues and organs while functioning close interacting to generate a protective response against invaders. Two components of immunity are recognized: innate and adaptive. T cell subtypes secrete variable cytokines that counter-regulate each other, and an imbalance between pro- and anti-inflammatory pathways is seen that plays an important role in the pathogenesis of neuropsychiatric disorders such as autism.

autism spectrum disorder (ASD) neuropsychiatric disorders cytokines

1. Major Histocompatibility Complex (MHC) and Autism Spectrum Disorder

The major histocompatibility complex (MHC) is a highly polymorphic cluster of genes with some of the greatest allelic diversity in the genome. MHC genes are both polygenic (containing multiple genes) and polymorphic (containing multiple variants of each gene). It is well known that MHC proteins mediate both the adaptive and innate immune responses [1][2][3]. There are multiple studies supporting the association of different genes with autism spectrum disorder (ASD) development, which also involve the function of the immune system. The human leukocyte antigen (HLA) alleles A2, Death Receptor (DR)4, and DR11 are associated with a diminished lymphocyte response and are involved in a major susceptibility for ASD [4][5][6][7][8]. Within the HLA class III region, there is a complement C4B null allele, resulting from duplications of C4A, that confers a relative risk of 4.3 for the development of ASD [9][10]. In addition, the serine and threonine kinase C gene PRKCB1, which is involved in both B-cell activation and neuronal function, has been linked to ASD in some studies [11][12][13][14]. Peripheral blood RNA expression studies demonstrated an upregulation of genes involved in innate immune activation through the natural killer (NK) pathway in individuals with ASD, a finding that was confirmed in functional studies using NK-cells [15]. Multiple altered gene-susceptibility, related to innate immune activation and the loss of adaptive immune regulation, has been suggested. For example, a disrupted transcription of phosphatase and tensin homolog (PTEN) genes (involved in T regulatory cell development) and reelin, the association of a met genetic variant with autism-associated maternal autoantibodies reactive to fetal brain proteins, and cytokine expression have been associated with ASD etiology [16][17].

On the other hand, the function of brain MHC molecules' expression and their role in CNS development and plasticity is less understood [18]. Although MHC class I (MHC-I) protein was historically thought to be absent from the surface of neurons, more current evidence indicates that MHC-I protein is expressed on the surface of axons and dendrites under a regulated distribution [7][19]. For example, MHC-I protein is located at synapses, both pre- and post-synaptically [17] and controls axonal and dendritic outgrowth. It also regulates, in a negative way, the initial establishment of connections in the CNS and regulates, in multiple ways, synaptic transmission in hippocampal and cortical neurons. The balance of excitation to inhibition on cortical neurons is altered by changing MHC-I levels [20], which from all these studies shows that MHC-I proteins bidirectionally regulate both the initial establishment and strength of synapses in the CNS. It accomplishes this in a region-specific manner and mediates homeostatic plasticity [21][22].

The role of MHC-I in limiting neural connectivity and function also may have deep implications for neurodevelopmental disorders and neuropsychiatric diseases [23]. Specific MHC-I haplotypes and mutations in MHC-I genes have been implicated in ASD [9][10]. MHC-I levels on neurons are regulated by cytokines [22][24][25][26], and cytokine levels are altered in the blood, brain, and cerebrospinal fluid (CSF) in many neurodevelopmental disorders [27][28][29][30]. This suggests a peripheral immune response influencing brain cytokines via blood–brain barrier transference in early development, which becomes an altered connectivity and/or function in the CNS through changes in MHC-I levels in disease. Functional polymorphisms of macrophage inhibitory factor (MIF), which has several effects on innate and adaptive immune responses, have also been associated with ASD individuals [29][31]. Increased sera concentrations of MIF are correlated with worsening behavioral assessments in individuals with ASD compared with their unaffected siblings [32]. Moreover, genes that can affect immune responses, such as PTEN and reelin, have been associated with ASD [33][34][35][36][37], suggesting that multiple susceptibility genes related to innate immune activation and/or the loss of adaptive immune regulation may be involved in the etiology of ASD.

2. Adaptive Immune Reaction in Autism Spectrum Disorders

2.1. Cellular Immune Reaction in Autism

Earlier observations of immune pathology in ASD described a decreased lymphocyte response to mitogens in children with ASD and demonstrated the involvement of lymphocyte subsets in ASD pathology, finding a decreased number of these populations and an imbalanced ratio of helper/suppressor cells in these individuals [6][14]. Other studies confirming a lower helper/suppressor ratio with a decreased percentage of helper–inducer T cells and decreased percentage of cells positive to interleukin (IL)-2R under mitogenic stimulation were carried out to show an inversely correlated relationship with severity of autistic traits [38][39]. A significant increase in CD4+ memory and decrease in CD4+ naïve T cells associated with HLA A2-DR11 have also been observed in autism [40], as well as an imbalance of cytokines produced by CD4+ and CD8+ T cells with reported skewing toward Th2 response. This underlies a reduced proportion of CD4+ and CD8+ T cells producing IFN-γ and IL-2, which is in contrast with those T cells releasing other suppressor cytokines such as IL-4 [39][41]. T regulator cells (Tregs) play a key role in regulation of immune responses. Studies revealing a lower number of CD4+ CD25 high Tregs in the blood of

autistic children were reported by Mostafa and colleagues. This supports the reporting of allergic problems and family history of autoimmunity as risk factors for ASD since lower numbers of CD4+ CD25 high Tregs are seen in individuals with autism [40][41][42]. Dysregulation of Th1, Th2, Th17, and Treg-related transcription factors, and a deficit of forkhead box protein 3+ Tregs in combination with up-regulation of Th1/Th2/Th17-related transcription factors, were also described [29][41][42].

In the context of T- lymphocyte dysregulation occurring in a high number of autism subjects, the imbalances involved the abnormal T helper-suppressor cells ratio [43][44][45][46], a systemic deficit of regulatory T cells [24], and dysregulated cytokine release in ASD [47]. Therefore, the Th-17 lymphocytes subpopulation becomes relevant in the immune pahology this disorder.

In the interface between peripheral and CNS immunity, specific lymphocyte-derived cytokines impacting brain development, neural function, and behavior from specific subsets of lymphocytes work together to generate heterogeneous immune responses in brain [48]. Brain–peripheral interactions in neurodevelopmental disorders impact tissues via effector cytokines, such as IL-17A and IL-22. IL-17 is a critical mediator of neurodevelopmental abnormalities associated with maternal immune activation (MIA), and it has been found that IL-17 produced by maternal Th17 cells induces cortical malformations [49]. In addition, social behavioral defects mediated by the maternal microbiome and the gut microbiome are an increasingly recognized modulators of peripheral immune responses, and by extension of the brain, which promotes Th17 cell differentiation [26][45][50][51]. Similarly, the proinflammatory IL-6 cytokine derived from the placenta also has an impact on social behavior in autism [52][53].

In addition, Th17 CD4+ T cells are thought to be important players in autoimmune and neuroinflammatory diseases, and their product, IL-17A, is known to be up-regulated in several autoimmune systemic and neurological diseases [54][55][56]. Additionally, studies from different groups reveal significant changes to IL-17A in ASD with a positive correlation to severity [44], and the highest percentage of children are shown to share a severe form of the disease [57]. Upregulation of IL-17 was also found in ASD children with concomitant asthma [55][56], while the IL-23 cytokine, known to induce Th17 cell secretion of IL-17, was inversely found to be down-regulated in children at ASD onset, although it was positively associated with more impaired behavioral scores [43][58].

Frequently, ASD individuals are reported to have a higher concentration of proinflammatory or lower concentration of anti-inflammatory cytokines [44][59][60]. Mainly, the results show the pro-inflammatory cytokine profile in ASD, which involves IL-1 upregulation in connection with regression and is associated with enhanced level of IL-5 and IL-17 [61][62], which are involved in autoimmunity. Other changes in cytokine levels in ASD have been reported to be associated with severity, deficits in social sphere, impaired adaptive skills, and development [44]. Other studies have shown associations with hyperactivity, lethargy, and irritability [38][63][64][65]. IL-6 was strongly associated with ASD severity and deficits in social sphere, as well as a much greater alteration of intellectual quotient in those children with lower maximum levels [38][44][66]. Additionally, IL-6 is up-regulated, similar to IL-1, and has a significant correlation with hyperactivity, lethargy, and irritability [67].

Although without general consensus, ASD individuals are thought to have a higher concentration of pro-inflammatory or lower concentration of anti-inflammatory cytokines than healthy controls, as well as changes in S100 beta protein linked to glial function from peripheral blood analysis [44][68][69][70]. Some of these studies analyzed the correlation of behavioral profiles with immune abnormalities, ASD severity, and cytokine or chemokine abnormalities: an increased concentration of IL-1β, IL-6, IL-12p70, and TNF-α has been found [38][44][60][70]. In this context, IL-6 correlated positively with social impairments [71].

On the other hand, up-regulation of IL-1β, IL-10, monocyte chemoattractant protein (MCP), IL- 23, transforming growth factor (TGF)-β1, tumor necrosis factor (TNF)-α, and granulocyte macrophage colony-stimulating factor (GM-CSF)-1 were also described in relation to social dysfunction from several research groups [38][72][73][74]. Furthermore, stereotypic behavior, a core symptom of autism, seemed to correlate with down-regulation of TGF-β1 and GM-CSF, as well as up-regulation of IL-1β, IL-6, IL-8, IL12p40, TNF-α, and interferon (IFN)-γ [72][73]. Surprisingly, exacerbations of hyperactivity were found to be linked to low levels of anti-inflammatory cytokines (IL-10 and TGF-β), high levels of pro-inflammatory cytokines (IL-1β and IL-6) [60][68], several chemokines (IL-8, RANTES, and eotaxin), low levels of chemokine ligand (CXCL)-5 and IL-13, and high levels of IL-12p40 [72][75]. An interesting observation about sleep disturbances and aggressive behavior in ASD was made by Careaga et al., who found up-regulation of IL-1β, IL-6, IL-10, and MCP-1 in these ASD children, and, in particular, Th-1 skewed response was associated with more severe developmental impairment [38].

Understanding the differences and interactions between the peripheral nervous system and CNS is crucial for determining novel therapeutic strategies in ASD. A relevant insight into ASD pathogenesis was achieved through cytokine studies on autistic brains, as well as several immune phenotypes derived from the studies of peripheral blood soluble factors that correlate with increased or/and severe behavioral impairments of the disorder [76]. In this context, it has been concluded that ASD may be linked to a disturbed immune balance involving both of the main dysregulations focused on pro-inflammatory mediators, as well as anti-inflammatory cytokines and autoimmunity [77].

2.2. Adaptive Immune Response in Autism

Antibody Reaction in ASD Brain Tissue

In addition, abnormal immune responses in brain tissue have been demonstrated by an altered reaction to antigens, such as human myelin basic protein (MBP), in autistic brain, and the detection of enhanced MBP and anti-serotonin 5HT1A receptor autoantibodies in brain tissue. Although without a total consensus from different research groups, it has been suggested that there is a connection between autism, serotonin, and MBP [71][75][78]. Other laboratory data support the autoimmune hypothesis in the pathogenesis of autism based on the cerebrospinal fluid findings of elevated levels of autoantibodies to MBP and serological antibodies to measles virus, supporting the autoimmune pathogenesis of the disorder [79][80]. The detection of significantly increased autoantibodies to glial fibrillary acidic protein and to neuro-axon filament protein in autistic patients, as well as a particular association between the elevated levels of serum measles antibodies and human herpesvirus-6, with

brain autoantibodies in autism is also supportive of the viral hypothesis of autoimmune response induction of ASD [81], although it is clear that the subsequent activation of cytokines is the damaging factor associated with autism [77].

Peripheral Immunoglobulins Response in Autism

The majority of studies assessing B-cell number and function in autism have seen abnormalities; however, some peculiarities have been published that show only a significantly higher number of B cells but not of B cell function in children with ASD [82][83].

A selective deficiency of serum immunoglobulin (Ig) A in both children and adults with ASD compared to controls is accompanied by an upregulated expression of CD23+ B lymphocytes in children with the regressive form of disease [65]. Plasma levels of Igs in ASD reveal a reduced level of IgG and IgM isotypes inversely correlated with scores on lowest IgG levels but without B-cell dysfunction [42][84]. Higher concentrations of IgA, IgG, and IgE food-specific antibodies are also described in ASD [32][85].

Levels of IgG4 and IgG1 subclasses are increased in ASD individuals, with differences in IgA, IgG2, and IgG3 observed between ASD children and healthy family members [51]. From these findings, the production of Ig isotype and subclasses in autism could be associated with a cytokine-related influence on autoimmune B cells but not linked to B cell dysfunction [86]. In addition, a higher frequency of D8/17 B lymphocytes was found in ASD subjects, particularly in subjects with a pattern of repetitive behaviors. It was also found that B cells were hypersensitive to the vaccine preservative thimerosal, which could be revealing in the context of vaccination in these patients [87]. In the context of autoantibodies, this impact in the brain of individuals with autism was seen in patients with more severe cognitive and behavioral profiles [85][88].

Maternal Autoantibodies Influencing Gestational Environment in Risk for Autism Spectrum Disorder

The long list of serum autoantibodies in autism includes antibodies to ganglioside M1, the most abundant sialylated glycosphingolipid component of neuronal membranes. Mostafa and Al-Ayadhi (2011) found significantly higher amounts of these autoantibodies in children with ASD compared to controls, with the highest levels seen in the most severe cases of ASD [86]. These autoantibodies to gangliosides are frequently observed in autoimmune disorders associated with neurological impairment, such as SLE and Guillain-Barré syndrome [89][90]. Immunoreactivity to autoantibodies in children with ASD also include those specific to cardiolipin, phosphoserine, and α2-glycoprotein 1, as identified by Careaga and colleagues, 2013 [91], and to myelin-associated glycoprotein [51], mitochondrial DNA, double stranded DNA, nucleus, and nucleosomes [92][93][94].

More recently, autoantibodies against folate receptor (FRA) have been recognized as impacting brain pathology and behavioral phenotypes in children with ASD. In 2013, Frye's research group found FRAs to be prevalent in up to 70% of children with ASD, including blocking and binding FRAs [95]. This research found improvement in communication, language, attention, and stereotypic behaviors in treated, compared with non-treated, ASD

individuals [95]. This was also reported by Ramaekers et al., this year, who identified a significantly higher prevalence of blocking FRA in ASD compared to non-autistic individuals with developmental delays [96]. At the same time, it has been suggested that the immunoreactivity to autoantibodies and a relationship with familial autoimmunity impact brain pathology and behavioral phenotypes in ASD [90][97]. However, autoantibodies in autism are not only restricted to maternal phenomenology [98]. It is now believed that the maternal immune system (MIS) during fetal development is highly active and dynamic. It interacts with fetal immune cells to create a prenatal environment supporting pregnancy [99] but also influences programming of the fetal immune system [100][101].

During gestation, IgG antibodies are supplied to the fetus by the mother in a highly controlled manner mediated by neonatal Fc receptors (FcRn), an MHC class I (MHC-I)-related receptor [102][103]. However, during the antibodies' transplacental exchange, the prenatal environment could become altered, affecting fetal development and changing its susceptibility to neurodevelopmental disorders such as ASD [104]. This idea has been circulating since an early report focused on the family history of autoimmune disease indicated this as a strong risk factor for autism development [36][44], particularly due to maternal autoantibodies being transferred from mother to the fetal central nervous system (CNS), which could affect fetal brain development [105][106].

Several studies have documented a significant relationship between autoimmune disorders and increased risk of ASD, underlying a differential risk linked to the different maternal autoimmune diseases diagnosed during pregnancy. Thus, it recently has been inferred that folate receptor autoantibodies, which are prevalent in pregnancy and in developmental disorders such as autism, can block folate transport to the fetus and ultimately to the brain in young children, contributing to the core symptoms of autism [97]. This could contribute to autism by the fetus' exposure to maternal autoantibodies or due to an association with a family history of autoimmune disease by heritable factors. In both cases this would cause alterations in the maternal prenatal environment to drive risk for ASD [107][108]. Other evidence supports that trans placental passage of fetal brain-reactive antibodies can directly lead to ASD-like behavioral abnormalities in the offspring, such as hyperactivity and deficits in social interaction [44][109].

Further, families with at least one child with autism tend to display a high autoimmune burden such as type 1 diabetes, thyroiditis, and maternal rheumatoid arthritis. The risk of ASD in offspring is particularly increased when maternal autoimmunity is in an active phase during pregnancy [102], suggesting that an active inflammatory state during gestation may negatively influence the fetal neurodevelopmental trajectory.

As indicated above, there are a growing number of publications regarding shared genetic risk interacting with prenatal autoimmunity activation to support the immune hypothesis in autism. This risk is from the differential influence of the maternal and fetal immune environment from the different phenotypic clinical and evolutive courses of the disease. With this in mind, Meltzer and Van de Water, 2017, suggested that autism may result from maternal and/or host autoantibodies that selectively disrupt neural circuits regulating social behavior. In the context of maternal autoimmunity in ASD, several authors have revealed that a subset of mothers of children with ASD (10–12%) have been found to show immunoreactivity mediated by autoantibodies specific to fetal brain, inducing ASD-like pathology. This is seen in both human and in animal models [110][111][112][113][114]. During pregnancy, diseases

such as rubella, measles, or toxoplasmosis can also negatively impact early neurodevelopment of the fetus. It was reported by studies of pregnancy that history of viral and bacterial infections occurring in the first or third trimester, respectively, or maternal fever during gestation, showed a higher risk for later development of ASD in offspring [114][115]. From these findings, common immunopathological components may be overlapping in at-risk populations to generate neurodevelopmental and neurodegenerative disorders from the potential impact of the immune system disruptions occurring in early and late stages of life.

2.3. Innate Immunity in Autism Spectrum Disorder

Children with ASD have adverse reactions to benign factors such as immunizations, common illnesses, and environmental challenges [36][51][60][61][62][63][64][65][66][67][68][69][70][71][73][74][75][78][79][80][81][82][83][84][85][86][87][88][89][90][91][92][93][94][95][96][97][98][99][100][101][102][103][104][108][109][110][111][112][113][114][115][116]. Clinical reports suggest that aberrant behavior might be improved in some febrile ASD children.

2.3.1. Natural Killer Cells

Natural killer (NK) cells constitute about 15% of circulating lymphocytes and play a pivotal role in the innate immune system [117]. They secrete a cytokine profile that includes interferon gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), and IL-10, which have a cytolytic function as mediators of cellular cytotoxicity [118], as well as surveillance of immune function through crosstalk with dendritic cells [28][119][120]. Imbalances between their activation and inhibitory states could also play a role in autoimmune diseases, and although a specific mechanism is not clear, it could be linked to a dysregulated proinflammatory immune response [14]. An earlier report found NK cells associated with autism were focused on reduced NK cell activity, higher absolute numbers of NK cells in peripheral blood, and an increased expression of NK cell receptor RNA. Further, production of perforin, granzyme B, and IFN-γ in blood samples from these individuals was increased [118][120]. IL-15, a major NK cell stimulant, was significantly up-regulated in children with ASD [30][43][118][121] and was further increased in those with GI disturbances [122]. IL-12 is also increased at significant levels in plasma of autistic patients showing EEG abnormalities and GI complaints [57][116], as well as low Intelligence Quotient (IQ) and prominent aberrant behavior [62][71][123].

2.3.2. Monocytes

Monocytes are a part of an innate immune system and differentiate into macrophages. They migrate into the surrounding tissue, where they present antigens to lymphocytes that secrete proinflammatory mediators, such as IL-1β, IL-8 or TNF-α, in the course of systemic autoimmune or neurodegenerative disorders [28][124][125]. Increased levels of pro-inflammatory cytokines produced by peripheral blood mononuclear cells have been observed in individuals with ASD [14][57][121]. Monocytes in children with ASD may be positive for a surface receptor expressed on cells susceptible to apoptosis [64], and there is evidence that the differential LTR stimulations increase the concentration of several cytokines such as IL-1β, IL-6, and TNF-α. Other cytokines are decreased, such as IL-1β, IL-6, GM-CSF, and TNF-α, in ASD individuals, which may influence neuronal activity and drive autoimmunity [121][125][126][127][128]. Children with symptoms of irritability, lethargy, or hyperactivity have also been shown to have

higher release of pro-inflammatory cytokines, as well as lower amounts of anti-inflammatory cytokine secretion, suggesting an active pro-inflammatory state is required to exacerbate the behavioral symptoms occurring in the autism disorder course [122][129].

2.3.3. Microglia

Microglia are the professional resident cells of innate immunity in the brain and are specialized tissue macrophages involved in synaptic and neuronal development. They have been shown to play an important role in the pathogenesis of neuropsychiatric disorders [130][131]. The activation of microglia has been linked to abnormal brain connectivity in children with ASD [57][132][133][134], and the crosstalk between the peripheral immune elements and microglia, as well as abnormal white matter connectivity, has been described in ASD, indicating these cells as a potential source for intervention [132][133][134][135].

An aberrant response from immune cells in the CNS includes microglial cells. These cells are the resident phagocytes of the CNS implicated in neuronal cell death, which is mediated by the actions of inflammatory cytokines and neuropeptides [133][134]. The inflammatory cytokines IL-1, IL-6, and TNFα can directly affect the brain and alter neurodevelopment to impact behavior [136]. The microglia make contact with neurons and glia, and, like macrophages in other tissues, they are programmed to adopt a particular brain state [137][138] and perform critical local immune functions during development in health and disease, which is relevant to psychiatric diseases [139]. Further, astrocytes are also implicated in the pathogenesis of many psychiatric disorders, particularly by their contributions to synapse formation, function, and elimination. They are also essential to the immune response [137][138][140]. Astrocytes can both secrete and sense immune signals, and they can produce cytokines that affect the function of microglia and other brain cells, which is relevant during homeostasis and in response to inflammation [128]. Increased levels of pro-inflammatory cytokines are observed in many brain regions, and significant innate immune activation is also observed, particularly in microglia and astroglia of individuals with ASD [105][139].

Several clinical studies have revealed a strong link between a pro-inflammatory cytokine profile and ASD [59][71][123][141]. Elevated levels of pro-inflammatory cytokines and a pro-inflammatory phenotype of microglia have been demonstrated in autistic patients [6][139][142] and experimental models, such as maternal immune activation, suggesting that a pro-inflammatory response in the fetal environment can cause behavioral changes that last well into adulthood [56][105].

References

1. Palmen, S.J.; van Engeland, H. Review on structural neuroimaging findings in autism. J. Neural Transm. 2004, 111, 903–929.
2. Sinkus, M.L.; Adams, C.E.; Logel, J.; Freedman, R.; Leonard, S. Expression of immune genes on chromosome 6p21.3-22.1 in schizophrenia. Brain Behav. Immun. 2013, 32, 51–62.

3. Al-Hakbany, M.; Awadallah, S.; Al-Ayadhi, L. The relationship of hla class i and ii alleles and haplotypes with autism: A case control study. Autism Res. Treat. 2014, 2014, 242048.
4. Bennabi, M.; Gaman, A.; Delorme, R.; Boukouaci, W.; Manier, C.; Scheid, I.; Si Mohammed, N.; Bengoufa, D.; Charron, D.; Krishnamoorthy, R.; et al. Hla-class II haplotypes and autism spectrum disorders. Sci. Rep. 2018, 8, 7639.
5. Harville, T.; Rhodes-Clark, B.; Bennuri, S.C.; Delhey, L.; Slattery, J.; Tippett, M.; Wynne, R.; Rose, S.; Kahler, S.; Frye, R.E. Inheritance of hla-cw7 associated with autism spectrum disorder (asd). Front. Psychiatry 2019, 10, 612.
6. Needleman, L.A.; McAllister, A.K. The major histocompatibility complex and autism spectrum disorder. Dev. Neurobiol. 2012, 72, 1288–1301.
7. Torres, A.R.; Westover, J.B.; Rosenspire, A.J. Hla immune function genes in autism. Autism Res. Treat. 2012, 2012, 959073.
8. Sweeten, T.L.; Odell, D.W.; Odell, J.D.; Torres, A.R. C4b null alleles are not associated with genetic polymorphisms in the adjacent gene cyp21a2 in autism. BMC Med. Genet. 2008, 9, 1.
9. Warren, R.P.; Singh, V.K.; Cole, P.; Odell, J.D.; Pingree, C.B.; Warren, W.L.; White, E. Increased frequency of the null allele at the complement c4b locus in autism. Clin. Exp. Immunol. 1991, 83, 438–440.
10. Hashem, S.; Nisar, S.; Bhat, A.A.; Yadav, S.K.; Azeem, M.W.; Bagga, P.; Fakhro, K.; Reddy, R.; Frenneaux, M.P.; Haris, M. Genetics of structural and functional brain changes in autism spectrum disorder. Transl. Psychiatry 2020, 10, 229.
11. Hu, V.W. From genes to environment: Using integrative genomics to build a “systems level” understanding of autism spectrum disorders. Child Dev. 2013, 84, 89–103.
12. Philippi, A.; Tores, F.; Carayol, J.; Rousseau, F.; Letexier, M.; Roschmann, E.; Lindenbaum, P.; Benajjou, A.; Fontaine, K.; Vazart, C.; et al. Association of autism with polymorphisms in the paired-like homeodomain transcription factor 1 (pitx1) on chromosome 5q31: A candidate gene analysis. BMC Med. Genet. 2007, 8, 74.
13. Siniscalco, D.; Schultz, S.; Brigida, A.L.; Antonucci, N. Inflammation and neuro-immune dysregulations in autism spectrum disorders. Pharmaceuticals 2018, 11, 56.
14. Enstrom, A.M.; Lit, L.; Onore, C.E.; Gregg, J.P.; Hansen, R.L.; Pessah, I.N.; Hertz-Picciotto, I.; Van de Water, J.A.; Sharp, F.R.; Ashwood, P. Altered gene expression and function of peripheral blood natural killer cells in children with autism. Brain Behav. Immun. 2009, 23, 124–133.
15. Campbell, D.B.; Sutcliffe, J.S.; Ebert, P.J.; Militerni, R.; Bravaccio, C.; Trillo, S.; Elia, M.; Schneider, C.; Melmed, R.; Sacco, R.; et al. A genetic variant that disrupts met transcription is associated with autism. Proc. Natl. Acad. Sci. USA 2006, 103, 16834–16839.

16. Heuer, L.; Braunschweig, D.; Ashwood, P.; Van de Water, J.; Campbell, D.B. Association of a met genetic variant with autism-associated maternal autoantibodies to fetal brain proteins and cytokine expression. Transl. Psychiatry 2011, 1, e48.
17. Huh, G.S.; Boulanger, L.M.; Du, H.; Riquelme, P.A.; Brotz, T.M.; Shatz, C.J. Functional requirement for class I mhc in cns development and plasticity. Science 2000, 290, 2155–2159.
18. Needleman, L.A.; Liu, X.B.; El-Sabeawy, F.; Jones, E.G.; McAllister, A.K. Mhc class I molecules are present both pre- and postsynaptically in the visual cortex during postnatal development and in adulthood. Proc. Natl. Acad. Sci. USA 2010, 107, 16999–17004.
19. Glynn, M.W.; Elmer, B.M.; Garay, P.A.; Liu, X.B.; Needleman, L.A.; El-Sabeawy, F.; McAllister, A.K. Mhc class i negatively regulates synapse density during the establishment of cortical connections. Nat. Neurosci. 2011, 14, 442–451.
20. Goddard, C.A.; Butts, D.A.; Shatz, C.J. Regulation of cns synapses by neuronal mhc class i. Proc. Natl. Acad. Sci. USA 2007, 104, 6828–6833.
21. Autry, A.E.; Monteggia, L.M. Brain-derived neurotrophic factor and neuropsychiatric disorders. Pharmacol. Rev. 2012, 64, 238–258.
22. Drescher, H.K.; Bartsch, L.M.; Weiskirchen, S.; Weiskirchen, R. Intrahepatic th17/treg cells in homeostasis and disease—It's all about the balance. Front. Pharmacol. 2020, 11, 1598.
23. McAllister, A.K. Immune contributions to cause and effect in autism spectrum disorder. Biol. Psychiatry 2017, 81, 380–382.
24. Smith, S.E.P.; Li, J.; Garbett, K.; Mirnics, K.; Patterson, P.H. Maternal immune activation alters fetal brain development through interleukin-6. J. Neurosci. 2007, 27, 10695–10702.
25. Pentón-Rol, G.; Cervantes-Llanos, M.; Martínez-Sánchez, G.; Cabrera-Gómez, J.A.; Valenzuela-Silva, C.M.; Ramírez-Nuñez, O.; Casanova-Orta, M.; Robinson-Agramonte, M.A.; Lopategui-Cabezas, I.; López-Saura, P.A. Tnf-α and il-10 downregulation and marked oxidative stress in neuromyelitis optica. J. Inflamm. 2009, 6, 18.
26. Gonçalves Pereira, M.H.; Figueiredo, M.M.; Queiroz, C.P.; Magalhães, T.V.B.; Mafra, A.; Diniz, L.M.O.; da Costa, Ú.L.; Gollob, K.J.; Antonelli, L.V.; Santiago Hda, C. T-cells producing multiple combinations of infγ, tnf and il10 are associated with mild forms of dengue infection. Immunology 2020, 160, 90–102.
27. Xie, J.; Huang, L.; Li, X.; Li, H.; Zhou, Y.; Zhu, H.; Pan, T.; Kendrick, K.M.; Xu, W. Immunological cytokine profiling identifies tnf-α as a key molecule dysregulated in autistic children. Oncotarget 2017, 8, 82390–82398.
28. Li, X.; Chauhan, A.; Sheikh, A.M.; Patil, S.; Chauhan, V.; Li, X.M.; Ji, L.; Brown, T.; Malik, M. Elevated immune response in the brain of autistic patients. J. Neuroimmunol. 2009, 207, 111–

116.

29. Manzardo, A.; Henkhaus, R.; Dhillon, S.; Butler, M. Plasma cytokine levels in children with autistic disorder and unrelated siblings. Int. J. Dev. Neurosci. Off. J. Int. Soc. Dev. Neurosci. 2012, 30, 121–127.
30. Grigorenko, E.L.; Han, S.S.; Yrigollen, C.M.; Leng, L.; McDonald, C.; Mizue, Y.; Anderson, G.M.; Mulder, E.J.; de Bildt, A.; Minderaa, R.B.; et al. Macrophage migration inhibitory factor and stereotypical behavior in autism spectrum disorders. Pediatrics 2008, 122, e438–e445.
31. Bordeleau, M.; Fernández de Cossío, L.; Chakravarty, M.M.; Tremblay, M. From maternal diet to neurodevelopmental disorders: A story of neuroinflammation. Front. Cell. Neurosci. 2020, 14, 461.
32. Jaini, R.; Wolf, M.R.; Yu, Q.; King, A.T.; Frazier, T.W.; Eng, C. Maternal genetics influences fetal neurodevelopment and postnatal autism spectrum disorder-like phenotype by modulating in-utero immunosuppression. Transl. Psychiatry 2021, 11, 348.
33. Cuchillo-Ibáñez, I.; Andreo-Lillo, P.; Pastor-Ferrándiz, L.; Carratalá-Marco, F.; Sáez-Valero, J. Elevated plasma reelin levels in children with autism. Front. Psychiatry 2020, 11, 242.
34. Hernández-García, I.; Chamorro, A.J.; Ternavasio-de la Vega, H.G.; Carbonell, C.; Marcos, M.; Mirón-Canelo, J.A. Association of allelic variants of the reelin gene with autistic spectrum disorder: A systematic review and meta-analysis of candidate gene association studies. Int. J. Environ. Res. Public Health 2020, 17, 8010.
35. Ishii, K.; Kubo, K.; Nakajima, K. Reelin and neuropsychiatric disorders. Front. Cell. Neurosci. 2016, 10, 229.
36. Hughes, H.K.; Mills Ko, E.; Rose, D.; Ashwood, P. Immune dysfunction and autoimmunity as pathological mechanisms in autism spectrum disorders. Front. Cell. Neurosci. 2018, 12, 405.
37. Estes, M.L.; McAllister, A.K. Immune mediators in the brain and peripheral tissues in autism spectrum disorder. Nat. Rev. Neurosci. 2015, 16, 469–486.
38. Careaga, M.; Rogers, S.; Hansen, R.L.; Amaral, D.G.; de Water, J.V.; Ashwood, P. Immune endophenotypes in children with autism spectrum disorder. Biol. Psychiatry 2017, 81, 434–441.
39. Pardo, C.A.; Farmer, C.A.; Thurm, A.; Shebl, F.M.; Ilieva, J.; Kalra, S.; Swedo, S. Serum and cerebrospinal fluid immune mediators in children with autistic disorder: A longitudinal study. Mol. Autism 2017, 8, 1.
40. Chua, R.X.Y.; Tay, M.J.Y.; Ooi, D.S.Q.; Siah, K.T.H.; Tham, E.H.; Shek, L.P.C.; Meaney, M.J.; Broekman, B.F.P.; Loo, E.X.L. Understanding the link between allergy and neurodevelopmental disorders: A current review of factors and mechanisms. Front. Neurol. 2020, 11, 1965.
41. Xu, G.; Snetselaar, L.G.; Jing, J.; Liu, B.; Strathearn, L.; Bao, W. Association of food allergy and other allergic conditions with autism spectrum disorder in children. JAMA Netw. Open 2018, 1,

e180279.

42. Xie, S.; Karlsson, H.; Dalman, C.; Widman, L.; Rai, D.; Gardner, R.M.; Magnusson, C.; Schendel, D.E.; Newschaffer, C.J.; Lee, B.K. Family history of mental and neurological disorders and risk of autism. JAMA Netw. Open 2019, 2, e190154.
43. Sotgiu, S.; Manca, S.; Gagliano, A.; Minutolo, A.; Melis, M.C.; Pisuttu, G.; Scoppola, C.; Bolognesi, E.; Clerici, M.; Guerini, F.R.; et al. Immune regulation of neurodevelopment at the mother-foetus interface: The case of autism. Clin. Transl. Immunol. 2020, 9, e1211.
44. Pronovost, G.N.; Hsiao, E.Y. Perinatal interactions between the microbiome, immunity and neurodevelopment. Immunity 2019, 50, 18–36.
45. Marks, K.; Coutinho, E.; Vincent, A. Maternal-autoantibody-related (mar) autism: Identifying neuronal antigens and approaching prospects for intervention. J. Clin. Med. 2020, 9, 2564.
46. O'Rourke, J.A.; Ravichandran, C.; Howe, Y.J.; Mullett, J.E.; Keary, C.J.; Golas, S.B.; Hureau, A.R.; McCormick, M.; Chung, J.; Rose, N.R.; et al. Accuracy of self-reported history of autoimmune disease: A pilot study. PLoS ONE 2019, 14, e0216526.
47. 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 autismlike phenotypes in offspring. Science 2016, 351, 933–939.
48. Graham, A.M.; Rasmussen, J.M.; Rudolph, M.D.; Heim, C.M.; Gilmore, J.H.; Styner, M.; Potkin, S.G.; Entringer, S.; Wadhwa, P.D.; Fair, D.A.; et al. Maternal systemic interleukin-6 during pregnancy is associated with newborn amygdala phenotypes and subsequent behavior at 2-years-of-age. Biol. Psychiatry 2018, 83, 109–119.
49. Rudolph, M.; Graham, A.; Feczko, E.; Miranda-Dominguez, O.; Rasmussen, J.; Nardos, R.; Entringer, S.; Wadhwa, P.; Buss, C.; Fair, D. Maternal il-6 during pregnancy can be estimated from newborn brain connectivity and predicts future working memory in offspring. Nat. Neurosci. 2018, 21, 765–772.
50. Zerbo, O.; Leong, A.; Barcellos, L.; Bernal, P.; Fireman, B.; Croen, L.A. Immune mediated conditions in autism spectrum disorders. Brain Behav. Immun. 2015, 46, 232–236.
51. Ly, A.L.-A.; Mostafa, G.A. Serum antinucleosome-specific antibody as a marker of autoimmunity in children with autism. J. Neuroinflamm. 2014, 11, 69.
52. Zerbo, O.; Yoshida, C.; Gunderson, E.P.; Dorward, K.; Croen, L.A. Interpregnancy interval and risk of autism spectrum disorders. Pediatrics 2015, 136, 651–657.
53. Ly, A.L.-A.; Mostafa, G.A. Elevated serum levels of interleukin-17a in children with autism. J. Neuroinflamm. 2012, 9, 158.

54. Casanova, M.F.; Frye, R.E.; Gillberg, C.; Casanova, E.L. Editorial: Comorbidity and autism spectrum disorder. Front. Psychiatry 2020, 1273.
55. Rose, D.R.; Yang, H.; Careaga, M.; Angkustsiri, K.; Van de Water, J.; Ashwood, P. T cell populations in children with autism spectrum disorder and co-morbid gastrointestinal symptoms. Brain Behav. Immun.—Health 2020, 2, 100042.
56. Ly, A.L.-A.; Mostafa, G.A. Elevated serum levels of macrophage-derived chemokine and thymus and activation-regulated chemokine in autistic children. J. Neuroinflamm. 2013, 10, 72.
57. Masi, A.; Glozier, N.; Dale, R.; Guastella, A.J. The immune system, cytokines, and biomarkers in autism spectrum disorder. Neurosci. Bull. 2017, 33, 194–204.
58. Jyonouchi, H.; Geng, L.; Davidow, A.L. Cytokine profiles by peripheral blood monocytes are associated with changes in behavioral symptoms following immune insults in a subset of asd subjects: An inflammatory subtype? J. Neuroinflamm. 2014, 11, 187.
59. Enstrom, A.M.; Onore, C.E.; Van de Water, J.A.; Ashwood, P. Differential monocyte responses to tlr ligands in children with autism spectrum disorders. Brain Behav. Immun. 2009, 24, 64–71.
60. Napolioni, V.; Ober-Reynolds, B.; Szelinger, S.; Corneveaux, J.J.; Pawlowski, T.; Ober-Reynolds, S.; Kirwan, J.; Persico, A.M.; Melmed, R.D.; Craig, D.W.; et al. Plasma cytokine profiling in sibling pairs discordant for autism spectrum disorder. J. Neuroinflamm. 2013, 10, 38.
61. Yang, Y.; Shen, C.; Li, J.; Yuan, J.; Wei, J.; Huang, F.; Wang, F.; Li, G.; Li, Y.; Xing, L.; et al. Plasma IP-10 and MCP-3 levels are highly associated with disease severity and predict the progression of covid-19. J. Allergy Clin. Immunol. 2020, 146, 119–127.e114.
62. Suzuki, K.; Matsuzaki, H.; Iwata, K.; Kameno, Y.; Shimmura, C.; Kawai, S.; Yoshihara, Y.; Wakuda, T.; Takebayashi, K.; Takagai, S.; et al. Plasma cytokine profiles in subjects with high-functioning autism spectrum disorders. PLoS ONE 2011, 6, e20470.
63. Bryn, V.; Aass, H.C.; Skjeldal, O.H.; Isaksen, J.; Saugstad, O.D.; Ormstad, H. Cytokine profile in autism spectrum disorders in children. J. Mol. Neurosci. 2017, 61, 1–7.
64. Ashwood, P.; Krakowiak, P.; Hertz-Picciotto, I.; Hansen, R.; Pessah, I.; Van de Water, J. Elevated plasma cytokines in autism spectrum disorders provide evidence of immune dysfunction and are associated with impaired behavioral outcome. Brain Behav. Immun. 2010, 25, 40–45.
65. Guloksuz, S.A.; Abali, O.; Aktas, C.E.; Bilgic, G.S.; Deniz, G.; Yildirim, A.; Kawikova, I.; Guloksuz, S.; Leckman, J.F. Elevated plasma concentrations of s100 calcium-binding protein b and tumor necrosis factor alpha in children with autism spectrum disorders. Rev. Bras. Psiquiatr. 2017, 39, 195–200.
66. Yang, C.J.; Liu, C.L.; Sang, B.; Zhu, X.M.; Du, Y.J. The combined role of serotonin and interleukin-6 as biomarker for autism. Neuroscience 2015, 284, 290–296.

67. Ferguson, B.J.; Marler, S.; Altstein, L.L.; Lee, E.B.; Mazurek, M.O.; McLaughlin, A.; Macklin, E.A.; McDonnell, E.; Davis, D.J.; Belenchia, A.M.; et al. Associations between cytokines, endocrine stress response, and gastrointestinal symptoms in autism spectrum disorder. Brain Behav. Immun. 2016, 58, 57–62.
68. Ashwood, P.; Enstrom, A.; Krakowiak, P.; Hertz-Picciotto, I.; Hansen, R.L.; Croen, L.A.; Ozonoff, S.; Pessah, I.N.; Van de Water, J. Decreased transforming growth factor beta1 in autism: A potential link between immune dysregulation and impairment in clinical behavioral outcomes. J. Neuroimmunol. 2008, 204, 149–153.
69. Makinodan, M.; Iwata, K.; Ikawa, D.; Yamashita, Y.; Yamamuro, K.; Toritsuka, M.; Kimoto, S.; Okumura, K.; Yamauchi, T.; Yoshino, H.; et al. Tumor necrosis factor-alpha expression in peripheral blood mononuclear cells correlates with early childhood social interaction in autism spectrum disorder. Neurochem. Int. 2017, 104, 1–5.
70. Han, Y.M.; Cheung, W.K.; Wong, C.K.; Sze, S.L.; Cheng, T.W.; Yeung, M.K.; Chan, A.S. Distinct cytokine and chemokine profiles in autism spectrum disorders. Front. Immunol. 2017, 8, 11.
71. Libbey, J.E.; Coon, H.H.; Kirkman, N.J.; Sweeten, T.L.; Miller, J.N.; Stevenson, E.K.; Lainhart, J.E.; McMahon, W.M.; Fujinami, R.S. Are there enhanced mbp autoantibodies in autism? J. Autism Dev. Disord. 2008, 38, 324–332.
72. Inga Jácome, M.C.; Morales Chacòn, L.M.; Vera Cuesta, H.; Maragoto Rizo, C.; Whilby Santiesteban, M.; Ramos Hernandez, L.; Noris García, E.; González Fraguela, M.E.; Fernandez Verdecia, C.I.; Vegas Hurtado, Y.; et al. Peripheral inflammatory markers contributing to comorbidities in autism. Behav. Sci. 2016, 6, 29.
73. Burgess, N.K.; Sweeten, T.L.; McMahon, W.M.; Fujinami, R.S. Hyperserotoninemia and altered immunity in autism. J. Autism Dev. Disord. 2006, 36, 697–704.
74. Sink, V.K. Phenotypic expression of autoimmune disorder (aad): A major subset of autism. Ann. Clin. Psychiatry 2009, 21, 148–161.
75. Sink, V.K.; Lin, S.X.; Newell, E.; Nelson, C. Abnormal measles-munps-rubella antiboodies and CNS autoimmunity in children with autism. J. Biomed. Sci. 2000, 9, 359–364.
76. Weizman, A.; Weizman, R.; Szekely, G.A.; Wijsenbeek, H.; Livni, E. Abnormal immune response to brain tissue antigen in the syndrome of autism. Am. J. Psychiatry 1982, 139, 1462–1465.
77. Cohly, H.H.; Panja, A. Immunological findings in autism. Int. Rev. Neurobiol. 2005, 71, 317–341.
78. Singh, V.K.; Lin, S.X.; Yang, V.C. Serological association of measles virus and humanherpesvirus-6 with brain autoantibodies in autism. Clin. Immunol. Immunopathol. 1998, 89, 105–108.
79. Wasilewska, J.; Kaczmarski, M.; Stasiak-Barmuta, A.; Tobolczyk, J.; Kowalewska, E. Low serum iga and increased expression of cd23 on b lymphocytes in peripheral blood in children with

regressive autism aged 3–6 years old. Arch. Med. Sci. AMS 2012, 8, 324–331.

80. Heuer, L.S.; Rose, M.; Ashwood, P.; Van de Water, J. Decreased levels of total immunoglobulin in children with autism is not a result of b cell dysfunction. J. Neuroimmunol. 2012, 251, 94–102.
81. Rossignol, D.A.; Frye, R.E. A systematic review and meta-analysis of immunoglobulin G abnormalities and the therapeutic use of intravenous immunoglobulins (ivig) in autism spectrum disorder. J. Pers. Med. 2021, 11, 488.
82. Heuer, L.; Ashwood, P.; Schauer, J.; Goines, P.; Krakowiak, P.; Hertz-Picciotto, I.; Hansen, R.; Croen, L.A.; Pessah, I.N.; Van de Water, J. Reduced levels of immunoglobulin in children with autism correlates with behavioral symptoms. Autism Res. 2008, 1, 275–283.
83. Spiroski, M.; Trajkovski, V.; Trajkov, D.; Petlichkovski, A.; Efinska-Mladenovska, O.; Hristomanova, S.; Djulejic, E.; Paneva, M.; Bozhikov, J. Family analysis of immunoglobulin classes and subclasses in children with autistic disorder. Bosn. J. Basic Med. Sci. 2009, 9, 283–289.
84. Piras, I.; Haapanen, L.; Napolioni, V.; Sacco, R.; Van de Water, J.; Persico, A. Anti-brain antibodies are associated with more severe cognitive and behavioral profiles in italian children with autism spectrum disorder. Brain Behav. Immun. 2014, 38, 91–99.
85. Mostafa, G.A.; Al-Ayadhi, L.Y. Increased serum levels of anti-ganglioside m1 autoantibodies in autistic children: Relation to the disease severity. J. Neuroinflamm. 2011, 8, 39.
86. Bobrowski-khoury, N.; Ramaekers, V.; Sequeira, J.M.; Quadros, E.V. Folate receptor alpha autoantibodies in autism spectrum disorders diagnosis, treatment and prevention. J. Pers. Med. 2021, 11, 710.
87. Racicot, K.; Kwon, J.Y.; Aldo, P.; Silasi, M.; Mor, G. Understanding the complexity of the immune system during pregnancy. Am. J. Reprod. Immunol. 2014, 72, 107–116.
88. Mostafa, G.A.; Al-Ayadhi, L.Y. The relationship between the increased frequency of serum antineuronal antibodies and the severity of autism in children. Eur. J. Paediatr. Neurol. 2012, 16, 464–468.
89. Kusunoki, S.; Kaida, K. Antibodies against ganglioside complexes in Guillain-Barre syndrome and related disorders. J. Neurochem. 2011, 116, 828–832.
90. Careaga, M.; Hansen, R.L.; Hertz-Piccotto, I.; Van De Water, J.; Ashwood, P. Increased anti-phospholipid antibodies in autism spectrum disorders. Mediat. Inflamm. 2013, 2013, 935608.
91. Mostafa, G.A.; Al-Ayadhi, L.Y. The possible relationship between allergic manifestations and elevated serum levels of brain specific autoantibodies in autistic children. J. Neuroimmunol. 2013, 261, 77–81.

92. Mostafa, G.A.; El-Sherif, D.F.; Al-Ayadhi, L.Y. Systemic autoantibodies in children with autism. J. Neuroimmunol. 2014, 272, 94–98.
93. Zhang, B.; Angelidou, A.; Alysandratos, K.D.; Vasiadi, M.; Francis, K.; Asadi, S.; Theoharides, A.; Sideri, K.; Lykouras, L.; Kalogeromitros, D.; et al. Mitochondrial DNA and anti-mitochondrial antibodies in serum of autistic children. J. Neuroinflamm. 2010, 7, 80.
94. Frye, R.E.; Sequeira, J.M.; Quadros, E.V.; James, S.J.; Rossignol, D.A. Cerebral folate receptor autoantibodies in autism spectrum disorder. Mol. Psychiatry 2013, 18, 369–381.
95. Ramaekers, V.T.; Quadros, E.V.; Sequeira, J.M. Role of folate receptor autoantibodies in infantile autism. Mol. Psychiatry 2013, 18, 270–271.
96. Aldo, P.B.; Racicot, K.; Craviero, V.; Guller, S.; Romero, R.; Mor, G. Trophoblast induces monocyte differentiation into CD14+/CD16+ macrophages. Am. J. Reprod. Immunol. 2014, 72, 270–284.
97. Braunschweig, D.; Ashwood, P.; Krakowiak, P.; Hertz-Picciotto, I.; Hansen, R.; Croen, L.A.; Pessah, I.N.; Van de Water, J. Autism: Maternally derived antibodies specific for fetal brain proteins. Neurotoxicology 2008, 29, 226–231.
98. Dekel, N.; Gnainsky, Y.; Granot, I.; Racicot, K.; Mor, G. The role of inflammation for a successful implantation. Am. J. Reprod. Immunol. 2014, 72, 141–147.
99. Albrecht, M.; Arck, P.C. Vertically transferred immunity in neonates: Mothers, mechanisms and mediators. Front. Immunol. 2020, 11, 555.
100. Ghosh, M.K.; Muller, H.K.; Walker, A.M. Lactation-based maternal educational immunity crosses mhc class i barriers and can impart th1 immunity to th2-biased recipients. J. Immunol. 2017, 199, 1729–1736.
101. Mor, G.; Cardenas, I. The immune system in pregnancy: A unique complexity. Am. J. Reprod. Immunol. 2010, 63, 425–433.
102. Edmiston, E.; Ashwood, P.; Van de Water, J. Autoimmunity, autoantibodies, and autism spectrum disorders (asd). Biol. Psychiatry 2017, 81, 383–390.
103. Clements, T.; Rice, T.F.; Vamvakas, G.; Barnett, S.; Barnes, M.; Donaldson, B.; Jones, C.E.; Kampmann, B.; Holder, B. Update on transplacental transfer of IgG subclasses: Impact of maternal and fetal factors. Front. Immunol. 2020, 11, 1920.
104. Gata-Garcia, A.; Diamond, B. Maternal antibody and asd: Clinical data and animal models. Front. Immunol. 2019, 10, 1129.
105. Estes, M.L.; McAllister, A.K. Maternal immune activation: Implications for neuropsychiatric disorders. Science 2016, 353, 772–777.

106. Jones, K.L.; Van de Water, J. Maternal autoantibody related autism: Mechanisms and pathways. Mol. Psychiatry 2019, 24, 252–265.

107. Onore, C.; Enstrom, A.; Krakowiak, P.; Hertz-Picciotto, I.; Hansen, R.; Van de Water, J.; Ashwood, P. Decreased cellular il-23 but not il-17 production in children with autism spectrum disorders. J. Neuroimmunol. 2009, 216, 126–129.

108. Jyonouchi, H.; Geng, L.; Cushing-Ruby, A.; Quraishi, H. Impact of innate immunity in a subset of children with autism spectrum disorders: A case control study. J Neuroinflam. 2008, 5, 52.

109. Wu, S.; Ding, Y.; Wu, F.; Li, R.; Xie, G.; Hou, J.; Mao, P. Family history of autoimmune diseases is associated with an increased risk of autism in children: A systematic review and meta-analysis. Neurosci. Biobehav. Rev. 2015, 55, 322–332.

110. Martin, L.A.; Ashwood, P.; Braunschweig, D.; Cabanlit, M.; Van De Water, J.; Amaral, D.G. Stereotypies and hyperactivity in rhesus monkeys; exposed to IgG from mothers of children with autism. Brain Behav. Immun. 2008, 22, 806–816.

111. Braunschweig, D.; Golub, M.S.; Koenig, C.M.; Qi, L.; Pessah, I.N.; Van de Water, J.; Berman, R.F. Maternal autism-associated IgG antibodies delay developmentand produce anxiety in a mouse gestational transfer model. J. Neuroimmunol. 2012, 252, 56–65.

112. Bauman, M.D.; Iosif, A.-M.; Smith, S.E.P.; Bregere, C.; Amaral, D.G.; Patterson, P.H. Activation of the maternal immune system during pregnancy alters behavioral development of rhesus monkeyoffspring. Biol. Psychiatry 2014, 75, 332–341.

113. Atladóttir, H.Ó.; Thorsen, P.; Østergaard, L.; Schendel, D.E.; Lemcke, S.; Abdallah, M.; Parner, E.T. Maternal infection requiring hospitalization during pregnancy and autism spectrum disorders. J. Autism Dev. Disord. 2010, 40, 1423–1430.

114. Zerbo, O.; Iosif, A.M.; Walker, C.; Ozonoff, S.; Hansen, R.L.; Hertz-Picciotto, I. Is maternal influenza or fever during pregnancy associated with autism or developmental delays? Results from the CHARGE (Childhood Autism Risks from Genetics and Environment) study. J. Autism Dev. Disord. 2013, 43, 25–33.

115. Abel, A.M.; Yang, C.; Thakar, M.S.; Malarkannan, S. Natural killer cells: Development, maturation, and clinical utilization. Front. Immunol. 2018, 9, 1869.

116. Kucuksezer, U.C.; Aktas Cetin, E.; Esen, F.; Tahrali, I.; Akdeniz, N.; Gelmez, M.Y.; Deniz, G. The role of natural killer cells in autoimmune diseases. Front. Immunol. 2021, 12, 79.

117. Wu, Y.; Tian, Z.; Wei, H. Developmental and functional control of natural killer cells by cytokines. Front. Immunol. 2017, 8, 930.

118. Gładysz, D.; Krzywdzińska, A.; Hozyasz, K.K. Immune abnormalities in autism spectrum disorder-could they hold promise for causative treatment? Mol. Neurobiol. 2018, 55, 6387–6435.

119. Tye, C.; Runicles, A.K.; Whitehouse, A.J.O.; Alvares, G.A. Characterizing the interplay between autism spectrum disorder and comorbid medical conditions: An integrative review. Front. Psychiatry 2018, 9, 751.

120. Ashwood, P.; Krakowiak, P.; Hertz-Picciotto, I.; Hansen, R.; Pessah, I.N.; Van de Water, J. Altered T cell responses in children with autism. Brain Behav. Immun. 2011, 25, 840–849.

121. Edilova, M.I.; Akram, A.; Abdul-Sater, A.A. Innate immunity drives pathogenesis of rheumatoid arthritis. Biomed. J. 2021, 44, 172–182.

122. Laria, A.; Lurati, A.; Marrazza, M.; Mazzocchi, D.; Re, K.A.; Scarpellini, M. The macrophages in rheumatic diseases. J. Inflamm. Res. 2016, 9, 1.

123. Nagafuchi, Y.; Shoda, H.; Sumitomo, S.; Nakachi, S.; Kato, R.; Tsuchida, Y.; Tsuchiya, H.; Sakurai, K.; Hanata, N.; Tateishi, S.; et al. Immunophenotyping of rheumatoid arthritis reveals a linkage between hla-drb1 genotype, cxcr4 expression on memory CD4+ T cells, and disease activity. Sci. Rep. 2016, 6, 29338.

124. Raphael, I.; Joern, R.R.; Forsthuber, T.G. Memory CD4+ T cells in immunity and autoimmune diseases. Cells 2020, 9, 531.

125. Takai, C.; Matsumoto, I.; Inoue, A.; Umeda, N.; Tanaka, Y.; Kurashima, Y.; Wada, Y.; Narita, I.; Sumida, T. Specific overexpression of tumour necrosis factor-α-induced protein (tnfaip)9 in CD14+CD16− monocytes in patients with rheumatoid arthritis: Comparative analysis with tnfaip3. Clin. Exp. Immunol. 2015, 180, 458–466.

126. Grozdanov, V.; Bliederhaeuser, C.; Ruf, W.P.; Roth, V.; Fundel-Clemens, K.; Zondler, L.; Brenner, D.; Martin-Villalba, A.; Hengerer, B.; Kassubek, J.; et al. Inflammatory dysregulation of blood monocytes in parkinson’s disease patients. Acta Neuropathol. 2014, 128, 651–663.

127. Bernier, L.P.; York, E.M.; Kamyabi, A.; Choi, H.B.; Weilinger, N.L.; MacVicar, B.A. Microglial metabolic flexibility supports immune surveillance of the brain parenchyma. Nat. Commun. 2020, 11, 1559.

128. Eyo, U.B.; Wu, L.J. Microglia: Lifelong patrolling immune cells of the brain. Prog. Neurobiol. 2019, 179, 101614.

129. 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, 66.

130. Maezawa, I.; Calafiore, M.; Wulff, H.; Jin, L.W. Does microglial dysfunction play a role in autism and rett syndrome? Neuron Glia Biol. 2011, 7, 85–97.

131. Rodriguez, J.I.; Kern, J.K. Evidence of microglial activation in autism and its possible role in brain underconnectivity. Neuron Glia Biol. 2011, 7, 205–213.

132. Tsilioni, I.; Pantazopoulos, H.; Conti, P.; Leeman, S.E.; Theoharides, T.C. Il-38 inhibits microglial inflammatory mediators and is decreased in amygdala of children with autism spectrum disorder. Proc. Natl. Acad. Sci. USA 2020, 117, 16475–16480.

133. Dean, D.C.; Travers, B.G.; Adluru, N.; Tromp, D.P.; Destiche, D.J.; Samsin, D.; Prigge, M.B.; Zielinski, B.A.; Fletcher, P.T.; Anderson, J.S.; et al. Investigating the microstructural correlation of white matter in autism spectrum disorder. Brain Connect. 2016, 6, 415–433.

134. Lenz, K.M.; Nelson, L.H. Microglia and beyond: Innate immune cells as regulators of brain development and behavioral function. Front. Immunol. 2018, 9, 698.

135. Michell-Robinson, M.A.; Touil, H.; Healy, L.M.; Owen, D.R.; Durafourt, B.A.; Bar-Or, A.; Antel, J.P.; Moore, C.S. Roles of microglia in brain development, tissue maintenance and repair. Brain 2015, 138, 1138–1159.

136. Kim, Y.S.; Choi, J.; Yoon, B.E. Neuron-glia interactions in neurodevelopmental disorders. Cells 2020, 9, 2176.

137. Haruwaka, K.; Ikegami, A.; Tachibana, Y.; Ohno, N.; Konishi, H.; Hashimoto, A.; Matsumoto, M.; Kato, D.; Ono, R.; Kiyama, H.; et al. Dual microglia effects on blood brain barrier permeability induced by systemic inflammation. Nat. Commun. 2019, 10, 5816.

138. Davoli-Ferreira, M.; Thomson, C.A.; McCoy, K.D. Microbiota and microglia interactions in asd. Front. Immunol. 2021, 12, 2024.

139. Ashwood, P.; Corbett, B.A.; Kantor, A.; Schulman, H.; Van de Water, J.; Amaral, D.G. In search of cellular immunophenotypes in the blood of children with autism. PLoS ONE 2011, 6, e19299.

140. Depino, A.M.; Robinson-Agramonte, M.A. Understanding on Neuroimmunology in Autism Spectrum Disorder; Robinson-Agramonte, M.A., Ed.; Translational Approaches to Autism Spectrum Disorder; Springer International Publishing: Cham, Switzerland, 2015; Chapter 9; pp. 155–180.

141. Jones, K.L.; Croen, L.A.; Yoshida, C.K.; Heuer, L.; Hansen, R.; Zerbo, O.; DeLorenze, G.N.; Kharrazi, M.; Yolken, R.; Ashwood, P.; et al. Autism with intellectual disability is associated with increased levels of maternal cytokines and chemokines during gestation. Mol. Psychiatry 2017, 22, 273–279.

142. Sharon, G.; Cruz, N.J.; Kang, D.W.; Gandal, M.J.; Wang, B.; Kim, Y.M.; Zink, E.M.; Casey, C.P.; Taylor, B.C.; Lane, C.J.; et al. Human gut microbiota from autism spectrum disorder promote behavioral symptoms in mice. Cell 2019, 177, 1600–1618.e17.