# Immune Dysfunction in Autism: A Pathway to Treatment

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**Summary:** Autism is a complex and clinically heterogeneous disorder with a spectrum of symptoms. Clinicians, schools, and service agencies worldwide have reported a dramatic increase in the number of children identified with autism. Despite expanding research, the etiology and underlying biological processes of autism remain poorly understood, and the relative contribution from genetic, epigenetic, and environmental factors remains unclear. Although autism affects primarily brain function (especially affect, social functioning, and cognition), it is unknown to what extent other organs and systems are disrupted. Published findings have identified widespread changes in the immune systems of children with autism, at both systemic and cellular levels. Brain specimens from autism subjects exhibit signs of active, ongoing inflammation, as well as alterations in gene pathways associated with immune signaling and immune function. Moreover, many genetic studies have indicated a link between autism and genes that are relevant to both the nervous system and the immune system. Alterations in these pathways can affect function in both systems. Together, these reports suggest that autism may in fact be a systemic disorder with connections to abnormal immune responses. Such immune system dysfunction may represent novel targets for treatment. A better understanding of the involvement of the immune response in autism, and of how early brain development is altered, may have important therapeutic implications. **Key words:** Autism, immune system, autoimmunity, signaling pathways.

## HISTORICAL LINKS OF AUTOIMMUNITY AND AUTISM

Immunological dysfunction has been a recognized feature in autism spectrum disorders (ASD) for several decades, but controversy remains in terms of both its existence and its etiologic role. As early as 1971, a relationship between ASD and immune dysfunction was proposed by Money et al.,[1] who reported a familial link of polyendocrine autoimmune disorder with ASD. In more recent years, several epidemiologic studies have sought to determine if there is more than an anecdotal familial link between ASD and autoimmunity or immune dysfunction. Since 1999, at least eight studies have been conducted to address this issue. In seven of these studies, an association between familial autoimmunity and ASD was determined. In all but two of the studies,[2,3] however, the number of subjects was relatively small, and interpretation is compounded by the fairly low rate at which autoimmune diseases occur in the general population[4] (Table 1).

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The second major issue with these studies is the manner in which autoimmunity in families was determined. To date, the majority of studies have used self-reporting questionnaires, which are prone to inaccuracy and potential over-reporting. However, from a large population-based study (nearly 700,000 participants) in which both the ASD diagnosis and family history of autoimmune disease were obtained from medical records and not from surveys, Atladóttir et al.[2] found that some autoimmune disease were more common in parents of children with ASD. That study indicated increased rates of rheumatoid arthritis and celiac disease in mothers of children with ASD, and a higher rate of the autoimmune condition type 1 diabetes in both mothers and fathers. Similarly, in another large population-based case-control study, Croen et al.[3] found an increase in the autoimmune conditions of psoriasis and type 1 diabetes, as well as immune-mediated disorders such as asthma and allergies in mothers of children with ASD. That study was based on data recorded by physicians during the 4-year period surrounding pregnancy. Both of these large population-based studies support the theory that autoimmune responses and immune dysfunction at or around the time of pregnancy may be related to a later diagnosis of ASD in the offspring.

**Table 1.** *Epidemiological Studies of Autoimmunity and Immune dysfunction in Families of Children with ASD*

| References | Study population, no. | Reporting | Association with ASD? | Autoimmune diseases and immune dysfunction |
|---|---|---|---|---|
| Comi et al.[5] (1999) | 107 | Self-report | Yes | Rheumatoid arthritis (mat); general autoimmunity (mat, pat) |
| Sweeten et al.[6] (2003) | 303 | Self-report | Yes | Hypothyroidism and Hashimoto's thyroiditis (mat, pat); rheumatic fever (mat, pat) |
| Micali et al.[7] (2004) | 140 | Self-report | No | — |
| Croen et al.[3] (2005) | 2,520 | Medical records | Yes | Psoriasis (mat), asthma and allergies |
| Molloy et al.[8] (2006) | 308 | Self-report | Yes | Autoimmune thyroid disease (mat, pat)* |
| Mouridsen et al.[9] (2007) | 441 | Medical records | Yes | Ulcerative colitis (mat); type 1 diabetes |
| Valicenti-McDermott et al.[10] (2008) | 100 | Self-report | Yes | Rheumatoid arthritis (mat)†; celiac disease (mat)† |
| Atladóttir et al.[2] (2009) | 689,196 | Medical records | Yes | Rheumatoid arthritis (mat); celiac disease (mat); type 1 diabetes (mat, pat) |

ASD = autism spectrum disorder; mat = maternal (autoimmunity link in mothers); pat = paternal (autoimmunity link in fathers).
*Autoimmune thyroid disease was found to be associated with the families of children with regressive ASD. †Rheumatoid arthritis and celiac disease in this study were associated with language regression.

Nonetheless, given the diversity of autoimmune disorders associated with ASD in these two studies,[2,3] no clear link between specific autoimmune diseases and ASD is readily apparent. The data suggest that global immune dysfunction in mothers during pregnancy, rather than specific diseases, may be associated with increased risk for ASD. Furthermore, although in most studies the increased rate of autoimmunity was limited to the mothers, others have found this link present in the fathers as well, suggesting that not only the timing of immune responses but also underlying heritable immunogenetic factors could be contributing to both the autoimmunity and the ASD.

It is also possible that immune dysfunction is not linked with all forms of ASD, but is confined to a specific subphenotype of ASD or is associated with specific behavioral features. Molloy et al.[8] reported more frequent familial autoimmune thyroid disease in children diagnosed with a regressive form of ASD, compared with children diagnosed with an early-onset form. Identifying whether there are specific endophenotypes of ASD that are linked with autoimmunity and immune dysfunction will help to elucidate the mechanism involved, as well as potentially identifying those individuals who could benefit from therapeutic immune interventions.

## MATERNAL ANTIBODIES

The finding of an increased history of autoimmune disorders in families of children with ASD is provocative, but does not identify the specific mechanisms that play a role in the pathogenesis of the disorder. The maternal transfer of autoantibodies from the mother to child during pregnancy is well documented, and is associated with a number of factors that can affect both pregnancy and neonatal outcome.[11] The presence of autoantibodies directed against critical neuronal components of fetal brain extracts in a subset of mothers of ASD children provides supporting evidence that one potential mechanism linking maternal immune components with ASD involves the transfer of autoantibodies from mother to the developing fetus during pregnancy[15,16,17,20] (Table 2).

One possibility is that anti-fetal brain autoantibodies, found in approximately 12% of mothers of children with ASD, bind to their neuronal targets during development, thereby interfering with or altering neurodevelopment. The phenomenon of maternal autoantibodies affecting the health of offspring has been reported in mothers with systemic lupus erythematosus whose children are born with congenital heart block.[21–24] Furthermore, neurotoxic autoantibodies from patients with systemic lupus erythematosus transferred into pregnant mice result in abnormal brain development in the offspring.[25]

Although it is hard to reproduce exactly the core features of autism in animal models, certain behaviors associated with ASD can be replicated, such as repetitive behaviors, learning, and hyperactivity.[26] In one model, the transference of IgG isolated from mothers with children with ASD into rhesus macaque monkeys during midgestation resulted in distinct behavioral changes in the offspring, which were not observed in monkeys that received IgG from mothers of typically developing children or monkeys that were saline treated.[18] Similar experiments in mice show that behavioral changes are pro-

**Table 2.** *Autoantibodies Directed to Brain Proteins in Mothers of Children with ASD*

| References | Target of maternal antibodies | Tissue source |
|---|---|---|
| Warren et al.[13] (1990) | Lymphocytes from children with ASD | Peripheral blood from children |
| Dalton et al.[14] (2003) | Murine cerebellar Purkinje cells and brainstem neurons | Mouse* postnatal day 1 and adult brain |
| Zimmerman et al.[15] (2007) | Unknown 30 and >250 kDa proteins | Fetal, postnatal, and adult rat brain extracts |
| Croen et al.[12] (2008) | Unknown 37, 39, and 73 kDa protein | maternal blood; fetal brain extract |
| Braunschweig et al.[16] (2008) | Unknown 37 kDa and 73 kDa protein (no reactivity to adult brain) | Human fetal and adult brain extract |
| Singer et al.[17] (2008) | Unknown 36 and 39 kDa protein; unknown 73 kDa to rat embryo | Adult and fetal rat and human brain extracts |
| Martin et al.[18] (2008) | Unknown 60 and 73 kDa protein | Fetal brain extract, Rhesus macaques* |
| Singer et al.[19] (2009) | Microglia cells | embryonic mouse cortex, Mice* |

*Transfer of human maternal autoantibodies to pregnant animals.

duced after antibodies from mothers of children with ASD (but not antibodies from typically developing control subjects) are injected into mice during midgestation.[18,19]

Whether these behavioral changes are directly related to ASD or are themselves distinct phenomena is not clear. Nonetheless, these models suggest that antibodies isolated from mothers with ASD children may alter the course of early neurodevelopment, leading to changes in behavior in the offspring. Future studies will need to better characterize the behavioral changes evoked by these antibodies and their relevance to core features or symptoms of ASD, as well as the potential cellular targets of these antibodies. Although the frequency at which potential autoantibodies are present in mothers who have children with ASD is low, the significance of carrying these antibodies may be substantial[16] and presents an exciting avenue for screening and therapy.

## AUTOIMMUNITY AND IMMUNE DYSFUNCTION IN INDIVIDUALS WITH ASD

Observations of autoimmunity are not limited to families of the children with ASD. Numerous studies point to the presence of immune dysfunction in some children with ASD, much of which is consistent with autoimmunity (see review by Enstrom et al.[27]).

Autoimmune diseases appear to result from a complex interaction of environmental and genetic factors. Numerous genes are thought to be associated with an increased risk of developing certain autoimmune diseases. The human leukocyte antigen (HLA) genes are among the strongest predictors of risk for autoimmune conditions (see review by Fernando et al.[28]). Different HLA haplotypes are also associated with neurodevelopmental disorders, such as schizophrenia and ASD (Table 3).

In ASD, early findings by Stubbs et al.[30] suggested that mothers of children with ASD share HLA haplotypes with their children more often than do typically developing mother–child pairs. Further studies found that several HLA haplotypes, in particular HLA-DR4, occur more often in children with ASD than in the general population.[32,33,36,37]

The HLA genes are located within a large genomic region referred to as the major histocompatibility complex (MHC). This region contains numerous other genes, including the complement protein C4 gene (*C4A*; alias *C4B*), which is important for innate immunity. Allelic deficiencies in the this gene, as well as its protein product, have been reported in ASD.[40–42] In ASD children from Sardinia, Guerini et al.[38] found no apparent HLA linkage, but several microsatellite linkages within the MHC were associated with ASD. These data suggest that genetic abnormalities in the MHC are not solely confined to HLA genes themselves, but also include genes in near proximity. In addition, a number of other immune-related genes have been implicated in ASD, including macrophage migration inhibitory factor (*MIF*),[43] *MET* encoding tyrosine kinase,[44] the serine and threonine kinase C gene *PRKCB* (alias *PRKCB1*),[45] protein phosphatase and tensin homolog (*PTEN*),[46] and the reelin gene (*RELN*).[47–49]

It is not known whether immune activation plays an initiating or ongoing role in the pathology of ASD. Immune activation leading to inflammation can have serious detrimental effects and could lead to destruction of tissues. Increased immune activation is associated with a number of neurodegenerative disorders and is speculated to play a role in psychiatric disorders such as schizophrenia, obsessive compulsive disorder, depression, bipolar disorder, and Gilles de La Tourette disorder, as well as ASD. Elevated levels of inflammatory cytokines in the CNS could reflect an inflammatory process that might contribute to abnormal neurodevelopment as seen in ASD.

Increased levels of proinflammatory cytokines such as IL-6, TNF$\alpha$, and MCP-1 in brain specimens and CSF

**Table 3.** *Genetic Studies of Human Leukocyte Antigen (HLA) Haplotypes in Individuals with ASD*

| References | Association with ASD? | HLA | Study population, no. | Region |
|---|---|---|---|---|
| Stubbs et al.[29] (1980) | No | Not available | 20 families; 757 controls | Not specified |
| Stubbs et al.[30] (1985) | Yes | Shared HLA* | 52 families; 83 families (historical) | Oregon and southern California; United Kingdom |
| Spence et al.[31] (1985) | No | Not available | 27 families | Not specified |
| Warren et al.[32] (1992) | Yes | B44-SC30-DR4 | 21 families; 62 controls | Utah |
| Daniels et al.[33] (1995) | Yes | B44-SC30-DR4 | 44 families; 126 controls† | Utah |
| Warren et al.[34] (1996) | Yes | HLA-DRB1 | 45 subjects; 79 controls | Not specified |
| Rogers et al.[35] (1999) | No | Not available | 90 families | Not specified |
| Torres et al.[36] (2002) | Yes | HLA-DR4; HLA-DR13 (protective) | 103 families | Oregon and Utah |
| Lee et al.[37] (2006) | Yes and No‡ | HLA-DR4 | 16 and 33 families; 475 normal controls | Tennessee; United States |
| Guerini et al.[38] (2009) | No§ | Microsatellite regions | 37 families | Sardinia |
| Johnson et al.[39] (2009) | Yes | HLA-DR4‖ | 31 families | New Jersey |

*Stubbs et al.[30] found that mothers of children with ASD had similar HLA types more often than did typically developing mother–child pairs.
†Daniels et al.[33] added 23 new families to the 1992 cohort of Warren et al., and added 64 new control subjects.
‡Lee et al.[37] Differences were found between the geographical defined families and controls, but not between the geographical diverse families and controls.
§Guerini et al.[38] did not find an HLA linkage, but did find linkages to microsatellite regions in proximity to previously reported HLA linkages.
‖Johnson et al.[39] found that HLA DR4 was associated with mothers of children with ASD.

obtained from young and old individuals with ASD (age range 5–44 years) suggest that an active neuroinflammatory process is ongoing in ASD.[50] Studies that assess cytokine levels in the periphery have often shown similar increases in proinflammatory cytokines,[51–55] as well as decreases in anti-inflammatory cytokines such as IL-10[24,52] and TGF$\beta$.[56] However, not all studies have shown a consistent pattern of specific cytokines, and data so far collected suggest a complex pattern of immune activation that varies among different subgroups of individuals with ASD.

Several studies have focused on immunological responses to dietary proteins, such as gluten and casein. Jyonouchi et al.[57] found that peripheral blood mononuclear cells from children with ASD responded to gliadin, cow's milk protein, and soy by producing higher levels of inflammatory cytokines, compared with peripheral blood mononuclear cells from typically developing children. However, children in this study were selected on the basis of having previously seen behavior improvements on a restricted diet and may translate to a specific subgroup of ASD who have gastrointestinal (GI) symptoms. Studies looking at mucosal immune responses in children with ASD who have GI symptoms have shown increased infiltration of T-cell, monocyte, and eosinophil in the gut mucosa, prominent mucosal T-cell activation with increased TNF$\alpha$ but lower IL-10 production, and increased numbers of paneth cells, compared with non-inflamed control subjects or compared with children with celiac disease or inflammatory bowel diseases.[51,52,58,59]

Uncertainty remains as to how prevalent GI abnormalities in ASD are and how GI symptoms may relate to core features of ASD or associated behavioral symptoms. A few small studies suggest that GI symptoms in ASD may be related to symptoms of aggression and hyperactivity, and that in some cases individuals with ASD may benefit from immune therapies targeting GI issues (to resolve activated mucosal immune responses). According to one recent report, a case of celiac disease was mistaken for ASD; upon removal of gluten from the patient's diet, and implementation of a modified diet, behaviors improved.[60] Such studies suggest that an abnormal immune response, in this case to a dietary protein, could contribute to behavioral abnormalities associated with ASD.

The presence of antibodies directed against adult brain or CNS tissue but not fetal brain tissue has been repeatedly reported in children with ASD (see reviews by Enstrom et al.[27] and Wills et al.[61]). These antibodies have varied targets, including neurotransmitter receptors, neuronal proteins, and nuclear material (Table 4). It is not clear, however, whether these autoantibodies have direct pathogenic relevance or are instead secondary to previous cellular damage or inflammatory reactions. Although some investigators have analyzed whether antibodies are directed at specific targets, such as myelin basic protein or glial fibrillary acidic protein, to date no clear associations between ASD and specific antibodies have been replicated across studies. This lack of specificity may suggest that the antibodies are generated as a consequence of some previous indiscriminate damage that involves different brain or CNS targets, leading to the generation of a diverse array of antibody specificities, as seen in ASD. Alternatively, the presence of these

**Table 4.** *The Presence of Antibodies Directed Against Adult Brain or CNS Tissue in Children with ASD*

| Study investigators (year) | Antibody Directed Toward | Positive or Negative? |
|---|---|---|
| Todd et al.[62] (1985) | Serotonin receptor | Positive |
| Singh et al.[63] (1993) | Myelin basic protein (MBP) | Positive |
| Singh et al.[64] (1997) | Neuron-axon acidic protein (NAFP); glial fibrillary acidic protein (GFAP) | Positive |
| Singh et al.[65] (1998) | Myelin basic protein (MBP); neuron-axon filament | Positive |
| Evers et al.[66] (2002) | Heat shock protein 90 (HSP90) | Positive |
| Vodjani et al.[67] (2004) | Gliadin; cerebellar peptides; heat shock protein 60 (HSP60) | Positive |
| Singh et al.[68] (2004) | Caudate nucleus; cerebral cortex; cerebellum | Positive |
| Singh et al.[69] (2004) | Nucleus and laminin | Negative |
| Silva et al.[20] (2004) | Unknown ~20 kDa protein | Positive* |
| Connolly et al.[70] (2006) | Brain-derived neurotrophic factor (BDNF); endothelial cells (EC); myelin basic protein | Positive |
| Singer et al.[71] (2006) | Unknown 73 and 100 kDa proteins | Positive |
| Libbey et al.[72] (2008) | Myelin basic protein | Negative |
| Kirkman et al.[73] (2008) | Glial fibrillary acidic protein (GFAP) | Negative |
| Wills et al.[74] (2009) | Unknown 52 kDa protein | Positive |

*Silva et al.[69] found a positive finding for a ~20 kDa protein, but determined it not to be MBP.

autoantibodies could reveal a group of ASD subjects who are more prone to immune dysfunction. Notably, antibodies directed at gut epithelium have also been described in ASD children;[75] however, no link between gut and brain antibodies has yet been established.

## DEFICITS IN IMMUNE AND NEUROLOGICAL SIGNALING PATHWAYS

### The PI3K–Akt–mTOR pathway

In the past few decades, gene polymorphism and gene expression studies have revealed differences in ASD that seem to converge within common signaling pathways that are necessary for proper development and function of both the nervous system and the immune system. One such pathway is the mTOR pathway.[76] Single-gene mutations that affect the mTOR pathway have been implicated in several monogenic disorders with a high rate of ASD (Table 5). Furthermore, a number of other genetic mutations that are linked to or feed into this pathway have been found in genome-wide association and copy number variation studies in ASD.[80] Given the central role of this pathway, it is possible that many other rare gene variants could also exist that affect signaling through these pathways. Although these genetic differences are associated with a common pathway, they may exert an effect at different points and thus alter function and development in varied ways that could manifest as different endophenotypes within ASD.

Strikingly, many of the immune alterations seen in ASD could result from dysregulation of the mTOR pathway (FIG. 1). One of the earliest immune observations seen in ASD was reduced response to recall antigens.[81] Other investigators have seen similar results in response to T-cell mitogens.[82,83] As a central regulator of cell growth and metabolism, the mTOR pathway is intrinsically involved in both T-cell activation and anergy (i.e., a state of unresponsiveness),[84] and hence dysfunction in this pathway could result in the T-cell abnormalities previously seen in ASD. In addition, cell survival is heavily regulated by the mTOR pathway.[85] Dysregulated apoptosis in immune cells[86] and neuronal cells[87] has been described in ASD, which suggests that mechanisms controlling cell survival are altered. PTEN is a major upstream regulator in the mTOR pathway, and mutations in this protein are associated with higher rates of ASD.[46]

In an animal model with PTEN-deficient cells, Foxp3, a putative controller for the generation of regulatory T-cells, was found to be downregulated,[88] leading to decreased number of cells that suppress immune responses and thus favoring immune dysfunction, activa-

**Table 5.** *Monogenic Forms of ASD That Affect the mTOR Pathway*

| Disorder | Gene | Rate of ASD, % | Gene Function | Reference |
|---|---|---|---|---|
| Fragile X syndrome | *FMR1* | 30–60 | Translational repressor | Clifford et al.[77] (2007) |
| Tuberous sclerosis complex | *TCS1/2* | 25–50 | mToR repressor | Wiznitzer[78] (2004) |
| PTEN hamartoma tumor syndrome | *PTEN* | no data | Inhibitor of PI3K | Herman et al.[46] (2007) |
| Neurofibromatosis type 1 | *NF1* | 4 | Ras GAP | Williams and Hersh[79] (1998) |

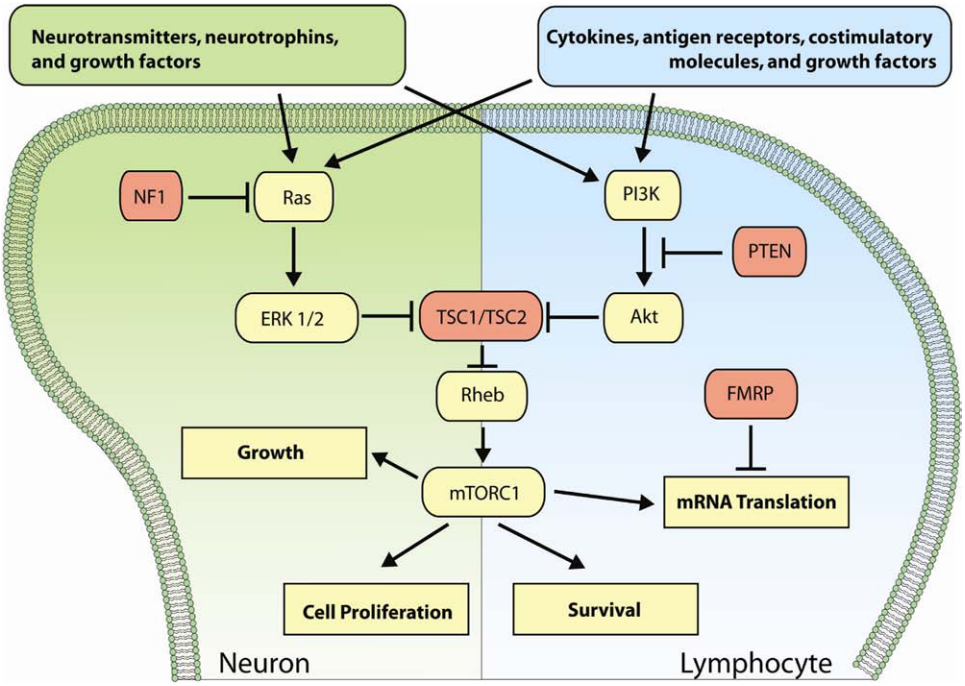


**FIG. 1.** mTOR signaling pathway in neurons and lymphocytes. Boxes shaded red indicate molecules known to be mutated in monogenic forms of autistic spectrum disorders.

tion, or both. A lack of immune regulation has been observed in ASD, as evinced by decreased plasma TGF$\beta$1 and decreased IL-10 producing T-cells.[51,52,56] Expression of FOXP3 has not yet been tested in ASD, but would be in line with mTOR dysregulation.[89]

In addition to abnormalities in the adaptive immune system in children with ASD, a number of differences have been noted in the innate immune system. Most relevant of these is the increase in proinflammatory cytokines, and the downregulation of IL-10,[51,55,90] findings that correspond to the function of monocytes where mTOR is inhibited.[91]

## Neurotransmitters

Similar to the immunological findings, neuropathological findings in ASD are numerous and varied (see review by Pardo and Eberhart[92]). Several studies have found increased brain size, brain structure differences, and reduced numbers of neurons in children with ASD, compared with control subjects.[93–95] Although no direct cause of these abnormalities is known, it has been suggested that a dysregulation in neurotransmission could result in altered development. Differences in neurotransmitters (including serotonin and GABA) and in glutamate signaling pathways have been demonstrated in ASD (see review by Lam et al.[96]).

A considerable body of research has addressed the role of the serotonin system in ASD, including increased peripheral blood platelet serotonin levels in ASD.[97,98] Serotonin has wide-ranging effects on physiological processes in the nervous, GI, and immune systems. Antibodies directed against serotonin receptors have also been reported in ASD,[62,99] suggesting that the availability of serotonin may be different in ASD. Depletion of tryptophan, the precursor to serotonin, has been linked to increases in behaviors associated with ASD.[100] The enzymes responsible for this conversion are under the control of cytokines such as IFN$\gamma$ and IL-1.[101,102] Thus, increased tryptophan degradation as a result of aberrant immune activation could affect serotonin levels and thus affect behavior.

In the CNS, glutamate is the major excitatory neurotransmitter and GABA is the major inhibitory neurotransmitter. Receptors for glutamate and GABA are present in lymphocytes, and both neurotransmitters have been shown to exert modulatory effects on the immune response.[103–105] Glutamate receptors are differentially expressed in activated versus naïve T-cells, and are believed to contribute to T-cell development and regulation.[106] In addition, glutamate can augment the production of cytokines by lymphocytes, as well as their migratory ability.[107,108]

GABA receptors appear to have an inhibitory function on immune responses in a subset of lymphocytes,[109] but may also increase pathogen clearance by macrophages.[110] Receptors for glutamate and GABA can act as targets for autoantibodies, resulting in symptoms associated with those often seen in ASD. For example, antibodies against glutamate receptors have been implicated in childhood seizure disorders,[112] a common comorbidity of ASD,[111,112] whereas antibodies against GABA recep-

tors are associated with motor disorders,[113] which are widely reported in ASD.[114] Although antibodies for either receptor family have not been detected in ASD, numerous unknown targets for autoantibodies exist, and it is possible that these could include subunits of the GABA or glutamate receptors. Dysregulation of neurotransmitter systems could further drive aberrant immune responses in ASD and could thus point to possible targets for therapeutic intervention.

## IMMUNE THERAPIES

Immune-based therapies have been suggested for ASD, but few have been tested. The suggested therapies are based largely on anecdotal observations, and very few rigorous placebo-controlled studies have been reported. It is estimated, however, that 50–70% of children with ASD undergo complementary and alternative medicinal therapies to treat their symptoms.[115–118] These therapies include the use of probiotics, anti-infectives, and dietary augmentation.[119] The clinical trials aimed at testing therapies that modulate the immune response in children with ASD often involve very few patients and lack appropriate controls.

Studies have addressed the use of steroids,[120–124] intravenous immune Ig,[125–127] antibiotics,[128] and vitamin D.[129] The findings vary, however, and often are contradictory. The modest but positive findings of improved behaviors in some studies suggest that a subgroup of individuals with ASD could benefit from immune-based therapies. Given the limitations of these studies, however, it is impossible to ascertain whether the benefits are real or merely placebo effects, as has been reported in other therapies for ASD.[130] Better patient selection with biological as well as behavioral assessment in the context of placebo-controlled studies that are conducted over sufficient periods of time are needed.

## CONCLUSION AND FUTURE DIRECTIONS

Immune abnormalities have been observed in ASD for many years. Although low patient numbers or poor choice of control subjects limit many of these observations, the general theme of immune dysfunction in ASD has been raised. Future work in the field will need to determine the extent of immune abnormalities in the broader ASD phenotype and whether immune dysfunction contributes to the etiology. Observations of autoantibodies directed against brain or other CNS components in children with ASD may help both in the diagnosis of subgroups of ASD and in identifying potential targets for therapies.

As understanding of ASD progresses, it appears more and more likely that there is no single cause of the disorder, whether on a genetic or an environmental level. Insights into the common signaling pathway disruptions seen in monogenic forms of ASD, as well as the role these pathways play in regulating the immune system, may provide clues to better understanding the biology of ASD, and a better understanding of the immune dysfunction seen in ASD would undoubtedly provide direction for investigating therapeutic strategies.

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