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Maternal Immune Activation and Autism Spectrum Disorder: Interleukin-6 Signaling as a Key Mechanistic Pathway

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Abstract
An emerging area of research in autism spectrum disorder (ASD) is the role of prenatal exposure to inflammatory mediators during critical developmental periods. Epidemiological data has highlighted this relationship showing significant correlations between prenatal exposure to pathogens, including influenza, and the occurrence of ASD. Although there has not been a definitive molecular mechanism established, researchers have begun to investigate this relationship as animal models of maternal infection have supported epidemiological findings. Several groups utilizing these animal models have found that activation of the maternal immune system, termed maternal immune activation (MIA), and more specifically the exposure of the developing fetus to maternal cytokines precipitate the neurological, immunological and behavioral abnormalities observed in the offspring of these animals. These abnormalities have correlated with clinical findings of immune dysregulation, neurological and behavioral abnormalities in some autistic individuals. Additionally, researchers have observed genetic variations in these models in genes which regulate neurological and immunological development, similar to what is observed clinically in ASD. Altogether, the role of MIA and cytokine dysregulation, as a key mediator in the neuropathological, behavioral and possibly genetic irregularities observed clinically in autism are important factors that warrant further investigation.

Introduction

Originally adapted form the Greek 'autos' or 'self', the term autism was first used in the early 1900s by Swiss psychiatrist Eugen Bleuler to describe a cluster of symptoms in schizophrenic individuals which included withdrawal or 'self-isolation' [1]. The term would later be used by Kanner in the 1940s, to describe a similar group of symptoms in children [1]. These early clinicians believed autism and the manifestations of social withdrawal to be the result of 'cold' unemotional parents. As a result, treatments for autism centered on medications such as lysergic acid diethylamide (LSD), electric shock and behavior change techniques, which encompassed pain and punishment therapy. As the understanding of the disorder

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evolved largely during the late 1990s, the role of behavioral therapy centered on the use of highly controlled learning environments, a form of therapy which has remained a key feature of autism therapy today. With an increased understanding of the disorder, clinicians began to characterize key phenotypes to aid in the assessment of individuals. With this came the inclusion of autism in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), as a behaviorally defined developmental disorder.

Today, the term autism is still used to describe the cluster of symptoms manifested in children displaying withdrawn or 'isolated' social behaviors, although classification and diagnostic criteria have evolved. Usually diagnosed during the first 3 years, early autistic patients often presented with a narrow range of symptoms, which often included moderate-to-severe mental retardation, although patients now present with symptoms that vary in both severity and combination with almost 30% of persons now having normal verbal expressions and IQ scores [2, 3]. These changes in clinical observations have led to the classification of autism as a spectrum disorder, autism spectrum disorder (ASD), which describes a group of developmental disorders characterized by impairments in reciprocal social interaction and verbal and nonverbal communication skills compounded by symptoms of restrictive and repetitive behaviors and/or stereotyped patterns of interest that are abnormal in their intensity or focus [4–7]. Included in this spectrum is 'classical' autism, which usually involves the stereotypical social isolation, impaired verbal communication and repetitive behaviors; Asperger syndrome, often described as a milder form of autism, lacking the components of intense repetitive behaviors and social withdrawal; and pervasive developmental disorder, which usually encompasses disorders that cannot otherwise be classified [2, 7–9].

These diagnostic changes in the clinical community, coupled with increased education and awareness among the clinical, research and general community, have also led to important changes in the epidemiological study of ASD. Previous epidemiological surveys, including those conducted prior to the classification of autism as a spectrum disorder, often used strict diagnostic criteria which resulted in the exclusion of individuals who would today be classified as autistic. These changes have led to increased research into the etiology of autism through the establishment of autism registries and the utilization of cohort studies. Although the exact etiology of the disorder has not been identified, potential environmental 'triggers', such as prenatal viral exposure, and genetic vulnerabilities, including mutations and polymorphisms in critical genes, have been among the epidemiological findings [10, 11]. Additionally, these studies have provided important information for the scientific community, which has begun to utilize animal models to investigate the role of environmental insults, such as prenatal viral exposure, in the etiology of autism. Several researchers have had promising results in this area not only confirming the potential for prenatal viral exposure to induce aberrant behavioral outcomes in offspring, but also the identification of the maternal cytokine response to viral pathogens, referred to as maternal immune activation (MIA) by Smith et al. [12], as a possible mechanism in the precipitation of these aberrant behaviors.

Despite this evidence, there is still disagreement within the research community concerning the environmental etiology of autism. Nevertheless, epidemiological and scientific observations supporting this role cannot be ignored, leading several researchers to conclude that certain 'environmental insults' may act as triggers, precipitating the development of autism. Furthermore, the lack of a single gene candidate and the observed genetic diversity within the autistic population have also led researchers to theorize that in genetically vulnerable individuals, environmental insults, such as prenatal viral exposure and resulting MIA, may explain the diverse behavioral phenotypes presented clinically in this spectrum disorder, as different genetic polymorphisms may differentially precipitate certain behavioral outcomes.

Environmental Theory of ASD: Epidemiological Perspective

Epidemiological studies have long been used in the investigation of diseases and disorders to deduce their etiology through the examination of trends, risk factors and commonalities in affected populations. Their application to neurodevelopmental disorders such as ASD has however had several obstacles including small sample sizes and changes in diagnostic criteria and classification systems. Early autism studies, for example, often utilized Kanner's autism criteria which employed strict diagnostic criteria encompassing narrow phenotypic ranges. The results were smaller sample sizes and lower observations of prevalence [13]. Today, with increased education and utilization of the DSM and the International Classification of Diseases criteria, researchers are more aware of the various phenotypic presentations seen within the autistic population, including more atypical types of autism. As a result, today's studies of-

ten encompass larger sample populations allowing for the collection of more statistically relevant data, although they have also resulted in perceived higher rates of prevalence than previous studies [7, 14–16]. In a comparative analysis by Kielinen et al. [17], for example, the Kanner and DSM criteria were used to assess the prevalence of autism within the same sample population, which revealed an increase in prevalence when the DSM criteria was used. As eluded to by Kielinen, these changes in prevalence may be attributable to methodological changes in these studies; changes in diagnostic, classification and inclusion criteria; and increased awareness and education among the clinical and general communities [17–19]. It is important to note that although an upward trend in prevalence has been observed, consistencies have remained in gender disparities as a higher rate of autism is reported in males throughout these studies [17, 20].

Epidemiological Studies: Genetic Predictors of ASD

Although changes within the field of ASD research have altered the way epidemiological surveys are conducted making chronological analysis of prevalence difficult, they have allowed for increased utilization of pregnancy/birth cohorts and other registries previously underutilized in the study of ASD. Additionally, dedicated autism registries now provide not only diagnostic and survey information, but often include biological specimens, such as serum samples, which can be utilized for biological assays and genetic analysis for commonalities within this population as well as divergences from control populations – all necessary information for the elucidation of the etiology of this disorder.

Genetic high-risk cohorts have been another resource utilized to examine the role of genetics in the etiology of ASD. These studies have differed from other areas, however, by utilizing sibling data rather than offspring. Through these studies, the genetic component of ASD has been shown as the recurrence rate in siblings, estimated at 3–8%, 60–90% for identical twins, show not only a strong genetic component but also a potentially significant role for epigenetic factors, including maternal inheritance and imprinting. Despite these findings, there has not been a 'single gene' candidate discovered for ASD, although several genes have been identified as abnormally expressed or polymorphic at a higher rate within the autistic population. Among these genes have been those involved in neuronal and synaptic formation and function, including reelin, neurogenin-1 and neuroligin-4, as well as those involved in immune regulation, such as cytokine receptor glycoprotein 130 (gp-130), although this gene product has been shown to possess several biological functions [21–25].

Epidemiological Studies: Environmental Predictors of ASD

The genetic diversity within the autistic population, in addition to the phenotypic variability observed clinically has posed a significant obstacle in identifying the etiology of ASD; however, it has led many researchers to examine alternative causative agents that may contribute to the neuropathology of this disorder. Researchers have now begun to utilize exposure-based high-risk cohorts, which are used to examine the effects of environmental risk factors on the etiology of disorders, to elucidate potential environmental etiologies of ASD. These cohorts not only examine environmental etiologies of disorders, but also how these environmental factors can interact with genes to precipitate these disorders, often creating diverse phenotypic presentations within a given disorder such as variations in symptom severity.

The utilization of these cohort studies, including the exposure risk cohort design, in the field of schizophrenia has identified several factors, including genetic polymorphisms and prenatal viral exposure, as significant risk factors in the etiology of this disorder [26–30]. Similarly, recent studies in ASD research, such as those examining prenatal exposure to rubella and other viral agents, have also alluded to a possible environmental etiology of ASD, and several researchers have seen significant correlations between prenatal exposure and the occurrence of this disorder in offspring [31–33]. It is important to note, however, that there have been several studies, such as the investigation of intrauterine human parvovirus infection by Anlar et al. [34], which have found no significant correlation between prenatal viral exposure and the occurrence of autism [34–37]. Nevertheless, several studies have shown significant correlations, primarily with prenatal rubella exposure and the development of autism. Most notable have been several studies by Chess [38, 39] who has found significant correlations with congenital rubella and the development of ASD. Other researchers have observed similar correlations with other viral pathogens including, herpes simplex, cytomegalovirus and varicella zoster [40–42]. Interestingly, Deykin and MacMahon [35], in a study which reported no association between prenatal viral exposure and the development of autism, actually reported an increased frequency of exposure in autistic subjects in comparison to control subjects. It is therefore plausible to theorize that an environmental insult, such as prenatal viral exposure, can act as a trigger

precipitating the aberrant behavioral phenotypes observed in ASD. This is not to say that an environmental etiology is the only contributor to the development of ASD. On the contrary, several researchers believe that these environmental triggers may exacerbate genetic vulnerabilities in some individuals, or may themselves cause alterations in gene and/or protein expression, precipitating the abnormal phenotypes observed in autistic individuals [11, 43, 44].

Evidence from Fetal Inflammatory Response Syndrome

The idea of an 'environmental insult' precipitating neurodevelopmental disorders is not a novel one as several compounds, including toxins and heavy metals, have been shown to cause neurological and congenital abnormalities in children exposed prenatally [45–48]. The link between inflammation and disruption in fetal development is also not a novel idea as several researchers have observed correlations between maternal infections, preterm births and neurological disorders in these preterm infants [11, 49–57]. Fetal inflammatory response syndrome (FIRS), commonly observed in spontaneous preterm labor and considered the fetal counterpart of systemic inflammatory response syndrome, is one example of how maternal infection can disrupt fetal development. [54, 58–60]. Researchers, such as Madsen-Bouterse et al. [58], have found that intrauterine infection is often a significant contributor to this syndrome with intra-amniotic infection and/or inflammation being present in one third of the patients with preterm labor. Usually the result of maternal bacterial infections, FIRS has been strongly associated with complications in preterm infants, including neurological disruption such as cerebral palsy and systemic FIRS in some instances [61–64]. Similarly, ASD has also been linked to maternal infection, as epidemiological studies have noted a strong correlation between maternal infection, particularly with pathogenic agents, and the occurrence of ASD and other developmental and psychiatric disorders in resultant offspring [65–69]. This research, compounded with clinical findings of immunological disruptions and increased serum cytokine levels in some autistic patients have driven the development of animal models to investigate the role of maternal infection in the etiology of ASD [70–74]. These studies have yielded several major findings: (1) maternal infection triggers an activation of the maternal immune system, termed MIA; (2) the resulting production of inflammatory cytokines can traverse the blood-placental barrier and activate the fetal immune system; and (3) this activation can lead to neurological and immunological disturbances that may precipitate the behavioral phenotypes observed clinically. These studies have also identified interleukin (IL)-6 as a key cytokine precipitating these events [12, 75–78].

The observations in ASD and models of MIA have been analogous to those seen in FIRS, as one of the diagnostic markers is an increase in IL-6 concentration in the umbilical cord plasma and/or the presence of funisitis, which is an inflammation of the connective tissue of the umbilical cord, as well as elevations in several other cytokines [12, 54, 58]. The parallels between these two disorders do not end at the neurological and immunological disruptions mediated by maternal infection and fetal exposure to maternally derived cytokines as several investigators have also observed genetic alterations, primarily in genes associated with immune regulation in FIRS infants, a feature also observed in autistic patients [11, 43, 58]. Altogether, these findings support a probable role of maternal infection in ASD and further suggest that maternally derived inflammatory cytokines can have deleterious and persistent effects on the developing fetus not only precipitating neurological and immunological abnormalities, but potentially altering the expression of genes important in immune regulation and neurodevelopment.

Prenatal Viral Exposure, MIA, Genetics and ASD

Genetic dysregulation has long been an area of interest in the study of ASD as there is a high degree of heritability observed in this disorder evidenced by the increased occurrence in siblings compared to the general population, estimated at 3–8% [79–82]. In comparison to other genetic disorders, this probability is still low, making the development of pedigrees difficult; however, a significant increase in the occurrence of the disorder in identical twins with a probability estimated at 60–92% has led many researchers and clinicians to utilize twin studies to investigate the role of genetics in ASD [80, 83, 84]. Interestingly, although the probability of the occurrence in fraternal twins is significantly lower than that of identical twins as expected, it has been shown to be greater than that observed in other sibling relationships, estimated at approximately 10%, suggesting a potential role for maternal and environmental influences [80, 84, 85].

In addition to familial inheritance, a strong occurrence of 'autistic-like' behaviors with genetic disorders, such as tuberous sclerosis and fragile X syndrome, has

strengthened the theory of a genetic mode of transmission. Approximately 18–33% of children with fragile X syndrome and an estimated 25–50% of children with tuberous sclerosis have some degree of ASD, although, like previously referenced sibling data, these estimates often vary as a result of differences in diagnostic criteria [24, 86–90]. Despite this high degree of comorbidity, only a small percentage of diagnosed ASD cases are attributable to these genetic disorders, with 6% of diagnosed autism cases due to fragile X syndrome and 1–4% to tuberous sclerosis [87, 90]. Together, these genetic disorders account for only 10% of diagnosed ASD cases, with the remaining 90% still of unknown etiology, although several other genes have been implicated as polymorphisms and abnormal expression patterns have been seen in several autistic individuals [80, 81, 87, 91]. Among those genes characterized are those involved in the development and function of the central nervous system (CNS), particularly those regulating neural differentiation, migration, axonal pathfinding and synapse formation. For example, the neuroligins, cell adhesion molecules involved in synaptic maturation and function, have been linked to autism as mutations and deletions in this gene have been observed within the autistic population [92]. Similarly, mutations in contactin-associated protein-like 2 (CASPR2), which interacts with neuroligins to promote synaptic function, have also been observed within the autistic population [92]. Another prominent gene linked to autism is reelin. Involved in neuronal migration, polymorphisms in this gene have been linked to autism, a finding largely supported by correlations between animal models of reelin mutations and postmortem analysis of autistic brains [92]. Additionally, genes involved in immune regulation, including IL-6, and genes important in several signal transduction pathways have also been shown to be differentially expressed in autistic individuals [93–98].

MIA: Cytokines and Genetics

Interestingly, researchers have observed neuropathological and genetic abnormalities similar to those observed in ASD in models of MIA and FIRS patients, suggesting early exposure to inflammatory cytokines may cause the abnormal expression of some genes (primarily those involved in immune and CNS regulation) [11, 12, 43, 58, 72, 99]. In FIRS, for example, genes involved in MCH antigen presentation, leukocyte adhesion and chemotaxis are differentially expressed in comparison to control patients, as are other immune regulatory factors including cytokines such as IL-6 [58]. In models of MIA, similar dysregulations have been noted for genes involved in immune regulation [11, 43, 68]. Utilizing the MIA model, researchers have also noted dysregulation in genes involved in the regulation of CNS development and function, including those involved in neural differentiation and migration, axonal pathfinding and synapse formation, maintenance and function, and neurotransmitter synthesis – genes which are also dysregulated in autistic individuals [11, 43, 68].

These observations have mirrored clinical findings in ASD; however, it is still unclear how these genetic abnormalities contribute to etiologic factors. Although described as a spectrum disorder, the range of phenotypes observed clinically do not correlate to the considerable genetic variations observed. Several researchers now hypothesize that certain genetic polymorphisms, which occur normally in the population and often have no pathological attributes, can in some individuals, when coupled with an environmental insult such as maternal infection and maternal cytokine exposure, lead to the development of different autistic phenotypes or ASD [100]. This theory has been used to explain the diverse genetic and phenotypic variations seen in autistic individuals, and it has been suggested that the risk of developing ASD as a result of maternal infection may be 3- to 7-fold higher in 'genetically susceptible' individuals. What this theory does not explain is the role played by maternal infection, or more specifically maternally derived inflammatory cytokines in altering the expression of certain genes (primarily those involved in regulation of immune and CNS development and function). Although research in FIRS and MIA models have shown that exposure to maternally derived inflammatory cytokines is sufficient to alter the expression of several immune related genes, the mechanism by which this is accomplished is still largely unknown.

IL-6 and Gene Expression

The answer to this question may lie in the innate ability of many cytokines to regulate gene expression through the activation of signal transduction pathways that ultimately activate transcription factors [101]. Cytokines such as IL-6, for example, activate Janus tyrosine kinase, mitogen-activated protein and/or other kinases, which in turn activate transcription factors such as signal transducer and activator of transcription (STAT) [101, 102]. These transcription factors in turn regulate the transcription of a range of gene products, binding to the corresponding gene promoter regions to induce or repress gene transcription [102]. During inflammation for example, IL-6-mediated STAT3 activation leads to the in-

creased expression of other cytokines and immune regulatory genes, and ultimately proteins [103–105]. In neurological disorders characterized by increased inflammation such as Alzheimer's disease, this increased activity leads to a persistent inflammatory state with corresponding morphological changes, including increased glial cell activity [106, 107].

These observations may explain the changes in gene expression seen in FIRS and ASD patients and animal models of MIA. In the fetal brain, exposure to maternally derived inflammatory cytokines may have effects similar to what is seen in these neurological disorders, precipitating the abnormal expression of fetal genes involved in the development and function of the immune system, such as what is observed in FIRS [78, 106, 108]. Similarly, cytokines have also been implicated in the regulation of genes involved in the development and function of the CNS, analogous to the way they regulate immunological genes [44, 108]. Cytokines such as IL-6, for example, can initiate the transcription of neural regulatory genes, important in the proliferation and differentiation of neural stem cells (NSC) through the activation of STAT3 and other transcription factors [44, 109]. In cases where maternally derived cytokines are present, this can lead to an increased activation and aberrant expression of these genes and the neurological and behavioral abnormalities observed clinically in ASD and models of MIA [11, 12, 50, 68]. It is therefore important not only to examine how certain genetic polymorphisms can predispose individuals to the development of ASD, but also how maternal cytokine exposure can act as a trigger for this disorder in susceptible individuals. It is equally important to examine how this exposure to maternal cytokines can disrupt the expression of important regulatory genes, and how these events affect the etiology and phenotypes of ASD, namely the variations in severity and combinations of signs and symptoms manifested clinically.

MIA, Neurodevelopment and ASD

Although the genetic component of ASD cannot be ignored, it has been accepted that maternal infection, or MIA, may be a significant contributor to the pathology of developmental disorders (e.g. ASD) and maternal cytokine expression and migration across the placenta, the main precipitator of the neurological, immunological and behavioral disruptions observed clinically [51, 54, 110–112]. Furthermore, this exposure to maternal cytokines has been shown to cause behavioral disruptions in offspring reminiscent of the phenotypes observed clinically in ASD, such as impaired social interaction [12, 50, 113]. In examining the potential mechanisms underlying this phenomenon, it is important to note the physiological significance of these molecules during key neurodevelopmental periods. Under normal physiological conditions, cytokines such as IL-6 are an important part of the neurodevelopmental signaling cascades involved in survival, proliferation, differentiation and phenotypic maintenance; regulation of neuronal migration and axonal pathfinding; and synapse formation and elimination [44, 101, 109, 112, 114–116]. Research has confirmed these physiological roles showing the regulation of NSC proliferation, survival and differentiation by the gp-130 family, BMP and members of the interleukin and interferon families [44, 101, 108, 109, 114, 117].

Cytokines and Neurodevelopment

During normal neurodevelopment, cytokines have been shown to be present and functional in the fetal brain, with receptors identified on both neuronal and glial cells [118]. Although present at minimal levels, these cytokines, such as IL-6 and its receptor, have been detected in the rat cortex as early as embryonic day 18, and in the human brain as early as 8 weeks [118–121]. Similarly, IL-1 has been detected in the embryonic rat brain, peaking during embryonic days 18–20 and again at postnatal day 7 [122]. Although the physiological role of these cytokines in the developing CNS is not fully understood, studies have confirmed that they function as important regulatory molecules and are involved in all phases of CNS development [44, 121, 123]. Their minimal concentrations also suggest that their regulatory activities may be closely related to circulating concentration, making the maintenance of homeostasis critical in maintaining the balance between their physiological and pathological activities. Several researchers have now begun to examine the physiological roles of these cytokines in an effort to better understand their pathological roles in ASD. Among those examined have been tumor necrosis factor (TNF), the interferons and interleukins; most notably IL-6 and other members of the gp-130 family, primarily due to their observed pleiotropic characteristics. Many of these cytokines, although originally defined as proinflammatory, have now been shown to also possess neurotropic properties regulating cell survival and proliferation in addition to differentiation and axonal guidance [44, 114, 117, 122, 124]. IL-6 for example has been shown to induce the differentiation of NSC into astrocytes and to a lesser extent neurons and oligodendrocytes while

promoting the survival of postnatal mesencephalic catecholoaminergic neurons and spinal cord cholinergic neurons in culture [125–128]. TNF-α and IL-1 have also been shown to have similar effects, specifically through IL-1 modulating the survival and growth of neuronal and glial cells, and TNF-α inducing synthesis of IL-6 from astrocytes and enhancing nerve growth factor release [122, 129, 130].

The activities of these cytokines observed in vitro are believed to mimic their physiological roles, although the mechanisms by which they exert their effects are still not fully understood. Contributing to this lack of understanding is the observed overlapping function of several of these cytokines, often able to elicit the same events, granted through different mechanisms. During CNS development, for example, cardiotrophin-1 appears to be the key cytokine inducing glial differentiation, although other members of the gp-130 family have been shown to be capable of accomplishing this [44, 114]. These redundant functions may explain why IL-6 has emerged as a key cytokine in disorders linked to maternal infection such as FIRS and ASD.

MIA and ASD: Potential Mechanisms

There has been tremendous research showing that several cytokines play an integral role in CNS development. There has also been research suggesting that even minute changes in the physiological concentrations of these cytokines (e.g. from maternal infections) can be deleterious to the developing fetus, leading to aberrant gene and protein expression as well as neurological, immunological and behavioral abnormalities. It is still unclear, however, how these effects are mediated as there remains disagreement concerning whether or not these maternal cytokines can traverse the placental barrier to induce responses in the fetal CNS. Several studies have yielded conflicting results as some suggest that only negligible levels of some cytokines pass this barrier, while others suggest that this does not occur. Whatever the mechanism, it is obvious that MIA somehow triggers activation of the fetal immune system as studies have shown increases in fetal cytokine expression in the CNS following exposure to maternal cytokines.

Cytokines and the Placental Barrier

Although there is disagreement as to whether or not cytokines can traverse the placental barrier, it has been well accepted that they are ubiquitously expressed in the placenta, where they serve an important role in the regulation of the maternal-fetal immune interface, aiding in preventing maternal rejection of the fetus through the regulation of the maternal immune system [131–133]. During pregnancy, the fetus, which produces alloantigens encoded by paternal genes, can illicit an immune response from the maternal immune system. Several researchers have hypothesized that instances of spontaneous abortions, aberrant fetal growth and recurrent miscarriages may be the result of the inability of the placenta to fully suppress this maternal response to these fetal alloantigens, allowing the maternal immune system to attack the developing fetus similar to what is seen in graft-versus-host rejections and other classical immunological responses to foreign invaders, such as pathogens [63, 134–136].

Therefore, the placenta functions as an important immune 'organ', coordinating maternal-fetal immune interactions in addition to furnishing the metabolic needs of the developing fetus. Among the resident immunological molecules in the placenta are maternal immune factors, including regulatory T cells (T_{reg}), human leukocyte antigen-G (HLA-G, a member of the MHC class 1 molecules) and T cell costimulatory molecules in addition to cytokines and other immune regulatory molecules that play an important role in regulating the maternal immune system, preventing the rejection of the developing fetus while still maintaining the capacity to defend the mother against pathogenic invaders [133, 135, 137]. Under normal conditions, there is an increase in the number of immunosuppressive T_{reg} preceding and after implantation of the fetus, which prevents the proliferation and activation of proinflammatory Th17 cells [138–142]. Several animal and clinical studies have confirmed this interplay, with observations of T_{reg} activity, correlated to increased uterine weight [141, 143, 144]. The role of resident cytokines becomes increasingly important during this process as several have been shown to be potent modulators of T cell regulations capable of shifting the balance between T_{reg} and Th17s, recruiting and maintaining the T_{reg} population in the placenta [145].

MIA and the Placental Barrier

The role of MIA in disrupting the balance between regulatory and proinflammatory T cells remains the focus of several studies as it is still unknown whether this event contributes to the phenotypes manifested in autistic patients. What has been shown is the role of cytokines, particularly IL-6, in maintaining the balance between T_{reg} and Th17s. IL-6, an important regulator in the tran-

sition from innate and adaptive immunity, is also a potent modulator of T cell function, shifting the balance from T_{reg} to Th17 cells, downregulating T_{reg} while promoting the differentiation of naive T cells into Th17 cells [146–148]. This relationship becomes particularly important when examined in the context of placental function and MIA. As mentioned previously, T_{reg} play an important role in maintaining tolerance during pregnancy while suppressing the activity of inflammatory Th17 cells, which have been implicated in autoimmune tissue injury. Here it can be appreciated that IL-6 expression, the result of MIA, can promote the expression of Th17 cells while downregulating T_{reg} expression compromising placental function while promoting a potential autoimmune response to the developing fetus [144, 149–151]. Observations of an increase in maternal antibodies against neuronal and lymphocytic markers in the serum of mothers of autistic children further strengthen this hypothesis, suggesting the involvement of a maternal immune response in precipitating this disorder [71, 110]. Additionally, potentially more significant have been observations of autoimmune disorders in a subset of autistic patients, termed Autoimmune Autistic Disorder (AAD). These patients exhibit increased proinflammatory cytokines and other immunological disruptions in Th1/Th2 ratios as well as auto-antibodies to brain myelin basic protein, phenomenons researchers have contributed to increases in Th17 cells potentially precipitated by prenatal viral infection [67, 71, 72, 152, 153]. Equally interesting are observations made in FIRS, including altered expression of genes associated with this arm of the immune system, including MHC antigen presentation, and leukocyte adhesion and chemotaxis [58]. Although more research is needed to make a direct correlation between these events and ASD, it is evident that maternal infection may impair the ability of the placenta to regulate the maternal immune system. It is also evident that resultant impairment of placental function may allow the passage of maternal cytokines, and/or elicit the induction of fetal inflammatory cytokines, which in turn disrupts important developmental pathways, primarily those involved in the development and function of CNS and immune system.

Despite these studies, there is still disagreement as to whether or not these maternal cytokines, produced during maternal infection, can traverse the placental barrier and disrupt normal fetal development. Research in FIRS has shown that in instances of maternal infection, the placenta can become inflamed, producing cytokines such as IL-6 which is a key biological marker in FIRS often detected in the amniotic fluid and maternal, fetal and umbilical cord serum [54, 58, 154, 155]. Nevertheless, research focusing on the placental migration of cytokines, following maternal infection continues to yield contradictory results as some researchers have observed minimal cytokine migration while others note that the levels that cross the placenta are too negligible to exert any effect. These contradictory findings may be attributed to variations in experimental design as comparative studies have shown that the ability of maternal cytokines to traverse the placental barrier may be highly dependent on the time of immune challenge. Independent work by several groups has shown that IL-6 can traverse the rat placenta to the fetus early in mid-gestation, approximately on embryonic days 11–13, while during embryonic days 17–19, this is not seen [156, 157]. This observation may explain epidemiological findings which suggest 2nd-trimester maternal infection pose the greatest risk for the development of ASD [158].

It is worthwhile to note, however, that even with no observable cytokine migration during late gestation, maternal infection during this period still results in an increase in cytokine levels in the fetal CNS as there have been observations of increased cytokine mRNA and protein levels, as well as other immunological disruptions in FIRS infants [54, 59, 78, 154]. Additionally, observations in models of MIA mimic FIRS findings of increased inflammatory cytokines and other immunological events in the fetal CNS in response to maternal injection, including the induction of monocyte chemoattractant protein-1 and increased glial cell reactivity [156, 157]. As LPS does not traverse the placental barrier, researchers have suggested the presence of intermediary mechanisms, possibly in the maternal-fetal interface, the placenta, that trigger these immunological responses in the fetal CNS. Whatever the exact mechanism, it is evident that maternal infection and MIA results in increased inflammation in the fetal CNS as well as changes in the transcription, expression and activity of factors that regulate the development and function of the CNS and immune system.

IL-6 and STAT3 and ASD

Although several cytokines have been found to be elevated in the fetal brain following exposure to maternal inflammatory cytokines, it has been proposed that IL-6 is the key cytokine responsible for precipitating the pathological effects observed in disorders such as FIRS and ASD. There have been several key pieces of evidence which have led to the identification of IL-6, including findings of increased IL-6 levels in the amniotic fluid of FIRS infants and its aberrant expression and/or function

in autoimmune disorders, some of which have been associated with ASD, as well as neurological disorders hallmarked by increased inflammation such as Alzheimer's disease [154, 159, 160]. Additionally, animal studies involving aberrant expression of IL-6 resulted in neurological disorders, with behavioral abnormalities analogous to clinical observations to disorders such as ASD [107, 161, 162]. However, models of MIA which have isolated IL-6 by selective inhibition of cytokines known to be elevated following maternal infection have been more convincing. In one model proposed by Smith et al. [12], single maternal injections of several cytokines were coadministered with their corresponding blocking peptide. Of these cytokines, only inhibition of IL-6 was sufficient to attenuate the behavioral, immunological and neurological abnormalities observed in offspring as a result of MIA. This study showed improvements in measures of social interaction, prepulse inhibition and latent inhibition, behavioral measures abnormal in ASD in adult offspring which were comparable to observations made in control animals [12].

The role of IL-6 as a key contributor to these pathologies is further strengthened when its physiological role is examined. As mentioned previously, IL-6 and other members of the gp-130 family maintain the proliferation and survival of NSC through activation of the STAT3 pathway. Additionally, these cytokines regulate neuronal and axonal pathfinding and the formation and maintenance of functional synapses. In vitro experiments and comparative in vivo analysis have demonstrated that many of these cytokines share redundant pathways and functions, activating analogous pathways to accomplish the same endpoint. Although an evolutionary favorable characteristic, it can be seen how pathological expression of these cytokines can lead to the dysregulation of these pathways. IL-6 for example has been shown to maintain the survival of and promote the proliferation of NSC in vitro, although in vivo experiments have shown that this may be accomplished by LIF and other members of the gp-130 family [44]. Furthermore, IL-6 has been shown to promote the differentiation of NSC in vitro, primarily promoting a glial phenotype although it has been shown to induce neuronal differentiation in NSC, and mimic the action of nerve growth factor in PC12 cells [109, 163, 164]. In vivo, however, the induction of gliogenesis is attributed to gp-130 family member, cardiotrophin-1 although studies have confirmed the presence of IL-6 receptors and IL-6 during early embryonic time points [44, 108]. It is plausible to hypothesize that during maternal infection, maternally derived IL-6 can traverse the placenta to act on the fetal brain, inducing the synthesis of fetal IL-6 and/or activating common pathways such as the STAT3 pathway as several studies have shown negligible migration of IL-6 preferentially to other cytokines [165, 166]. Once elevated, IL-6 can induce actions similar to those seen in vitro, such as increased cell survival and proliferation. Although in isolation or in conditions of neurological injury, these events may seem innocuous or even beneficial; during development, these events may lead to abnormal increases in neuronal and/or glial populations, as the negligible expression of cytokines, such as IL-6 in the fetal CNS, suggest that these processes are closely regulated by circulating concentrations of these cytokines. This situation can be put into perspective when we examine clinical observations of ASD, such as increased neuronal numbers in certain areas of the brain, which is believed to be a contributor to the behavioral abnormalities manifested in these patients.

The role of IL-6 in inducing differentiation, or regulating axonal guidance and synapse formation, can also be examined in the context of clinical observations. During normal CNS development, induction of differentiation is highly controlled, with neurogenesis preceding gliogenesis. These events are not only controlled by cytokine-induced activation of necessary pathways, but also by inhibition of transcription factors and methylation of gene loci [44]. During neurogenesis for example, STAT3, which has been shown to be a key transcription factor in the activation of gliogenic genes is inhibited, by protein modification in addition to other mechanisms. Similarly, gliogenic genes are methylated, preventing the binding of STAT3 and these genes [44]. As neurogenesis proceeds, proteins associated with embryonic neurons, such as cardiotrophin-1 accumulates, activating the STAT3 pathway [167]. This event coincides with the demethylation of gliogenic genes as well as the inhibition of neurogenic transcription factors. With pathological IL-6 expression, such as that derived from maternal sources, premature differentiation can mean disruption in neuronal or glial populations. These events can also lead to disruption of other important processes such as neuronal migration, axonal pathfinding and synapse formation. Several researchers hypothesize that these neurological events precipitate resultant behavioral abnormalities observed clinically in autistic patients. These findings not only implicate a potential 'trigger' for the development of ASD, but also identify potential biological markers which may be utilized to diagnose this disorder at earlier time points similarly to clinical diagnosis of FIRS. Early diagnosis does not necessarily mean early intervention, but the

identification of a biological marker may enable the use of pharmacological intervention in the management of this disorder.

Viral Pathogens, MIA and ASD

To date several researchers have cited a viral-induced activation of the maternal immune system, MIA, as the primary contributor to the behavioral abnormalities observed in animal models of MIA and in ASD [68]. Smith et al. [12], utilizing an animal model of MIA have strengthened this hypothesis, finding that the activation of the maternal immune system in response to viral exposure is a key mechanism in precipitating the behavioral abnormalities in MIA offspring. Furthermore, this group identified IL-6 as a key cytokine in this mechanism as inhibiting this cytokine attenuated the behavioral abnormalities observed in offspring exposed to MIA prenatally [12]. Other groups, however, have cited a potential alternative mechanism to the changes seen in these offspring, citing the actions of the viral pathogen itself as a key precipitator in ASD neuropathologies. In a study in which pregnant mice were injected with human influenza at embryonic day 9, Fatemi et al. [11] observed changes in protein expression in several key proteins involved in neurodevelopment, most notable of which was connexin 43. In another study by the same group, alternations in expression of several genes including those regulating myelin expression were also observed following prenatal viral infection [43, 168, 169].

It is important to note that although Smith et al. [12] and others cited increases in maternal cytokine levels, most notably IL-6, as a key factor in these disruptions, they also noted changes in gene expression following viral exposure. Additionally, in cases of FIRS, although immunological disruptions such as increased IL-6 levels were noted as one of the most significant characteristics, changes in gene expression were also observed in genes involved in immune regulation [58]. Fatemi's work does not preclude the role of the maternal immune response in precipitating the changes observed in models of MIA and clinically in ASD, but rather suggest the importance of examining the mechanistic aspects of viral activation of the immune system and the potential downstream effects on gene transcription and protein expression. It can be argued that either mechanism may be a precipitating factor as it is the initial viral exposure that initiates the activation of the maternal immune system and resultant inflammatory cascade. Although it is unclear whether the changes we observed in MIA and clinically in ASD can be attributed solely to either mechanism, or even whether these two can be separated, it is evident that prenatal viral exposure leads to an increase in maternal cytokine exposure and IL-6 levels and altered gene expression, and that these factors have the potential to precipitate the behavioral and neuropathologies observed clinically in ASD.

Current Therapeutic Approaches

Currently there is no cure for ASD and therapeutic intervention focuses primarily on the management of symptoms, utilizing behavioral therapy to control the abnormal behavioral phenotypes associated with the disorder. Although pharmacological intervention is not commonly used in the management of ASD, it is often utilized in the treatment of comorbid disorders, which frequently occur with ASD, including seizures, increased aggression and other pharmaceutically responsive conditions. The use of palliative care in the management of development disorders is not uncommon, as many, especially those of genetic origin are incurable, making the management of symptoms the only possible therapeutic intervention.

Recent research in ASD has highlighted the role of maternal infection in the etiology of ASD. More specifically, they have identified exposure to maternal cytokines, primarily IL-6, as a key environmental 'trigger' precipitating the development of ASD in some individuals. These findings are significant not only in understanding the etiology of ASD, but the identification of IL-6 may provide a potential biological marker enabling the early diagnosis of the disorder and earlier therapeutic intervention. The identification of IL-6 has also provided a potential therapeutic target as models of MIA have shown that inhibiting IL-6 during maternal infection can attenuate the behavioral abnormalities observed in MIA offspring. In studies by Smith et al. [12], coadministration of poly(I:C), used to induce MIA and IL-6 neutralizing antibody, attenuated the behavioral abnormalities observed in the offspring, as they observed improvement in prepulse inhibition and latent inhibition comparable to observations in control animals. Similarly, research by our group has also confirmed IL-6 as a potential therapeutic target, sufficient to attenuate the symptoms associated with ASD. Furthermore, we discovered that inhibition of IL-6-induced activation of STAT3 was also able to attenuate the behavioral and immunological abnormalities observed in MIA offspring. In vitro experiments utilizing an LPS-microglial model to induce inflammation showed that bioflavonoid pretreatment or cotreatment was sufficient to inhibit the produc-

tion of IL-6 and TNF-α, while IL-6 and bioflavonoid co-treatment of neuronal cultures showed that bioflavonoids could also inhibit IL-6-induced activation of STAT3 [113]. These results, which support previous findings by our group and others, suggest that bioflavonoid treatment not only has the potential to inhibit pathological cytokine production, but also to inhibit cytokine-induced activation of key signaling molecules such as STAT3 [170, 171]. Furthermore, in vivo experiments have shown similar results, with prophylactic bioflavonoid treatment reducing cytokine expression and STAT3 activity in MIA offspring [113]. These observations suggest that it is not only possible to attenuate the pathological increase in cytokine expression resulting from maternal infection, but therapeutic intervention to attenuate the resultant activation of critical signaling pathways may also be possible. These observations further suggest that prophylactic intervention may serve a protective role, especially in instances of known maternal infection. Similarly to how folic acid has been shown to be essential in the prevention of cephalic disorders, inhibition of pathological maternal cytokine expression may have therapeutic potential. Furthermore, postnatal bioflavonoid treatment to attenuate the activities of IL-6, such as pathological activation of STAT3 pathways, may prove to be of potential therapeutic value by providing more than a palliative treatment for ASD. Although these results are preliminary, and there are still many unanswered questions concerning the role maternal infection plays in precipitating ASD, it is evident that the IL-6 plays a key role in precipitating this disorder, making it a key target for therapeutic intervention. It is necessary not only to determine the mechanism by which maternal infection and IL-6 precipitate this disorder and how therapeutic intervention can aid in managing the symptoms associated with ASD, but also to attenuate the symptoms of this disorder.

Discussion

Since its first use in the early 1900s to describe a cluster of abnormal symptoms observed in a group of schizophrenics, and later similar symptoms in children, there have been significant advances in the understanding and treatment of ASD. There are still, however, many unanswered questions concerning the etiology of ASD as genetic variability among autistic individuals coupled with diverse phenotypic presentations have complicated the identification of a single causative agent. Nevertheless, researchers have made significant progress and have identified several genes differentially expressed in autistic individuals. Although these genes are not sufficient to cause ASD, they may provide a way to identify genetically susceptible individuals, or aid in the diagnosis of this disorder. Recently, maternal infection and fetal exposure to maternal cytokines, primarily IL-6, have been identified as potential environmental 'trigger', which, when coupled with certain genetic polymorphism, may lead to the development of ASD. Although the exact mechanism by which IL-6 elicits these events is unknown, its identification provides a potential diagnostic marker and therapeutic intervention point for ASD.

These advancements are promising; however, several unanswered questions still remain, prompting the need for more research. The identification of IL-6 as a potential trigger, for example, has raised questions concerning the ability of cytokines to traverse the placental barrier, and whether or not this passage is confined to certain developmental time points. Also unknown is whether or not the placenta itself contributes to the increase in fetal cytokine expression, as this has been observed in the absence of maternal cytokine migration. Researchers are also faced with the question concerning the mechanism by which IL-6 induces the abnormalities observed clinically in autism and whether or not inhibition of pathological IL-6 is sufficient to attenuate these abnormalities. It is also unclear as to whether or not maternally derived IL-6 is sufficient to promote the development of ASD or whether certain genetic polymorphisms are needed. Although animal models of MIA suggest that IL-6 is sufficient to induce the behavioral, immunological and neurological abnormalities observed in ASD, it is still unclear whether these findings completely mirror clinical observations. The role of genetics in the etiology of ASD also poses several questions including why some people, exposed prenatally to maternal cytokines may develop ASD while others do not.

As we investigate the etiology of this disorder, there are also important questions that arise concerning the diagnosis of this disorder. Although it is well accepted that autism is a part of a spectrum of disorders collectively referred to as ASD, there are some within the research and clinical community that would classify it as a syndrome, a singular manifestation of different disorders. This approach may explain the difficulty in determining the exact etiology of the disorder as well as the diversity of phenotypes presented clinically. Proponents of the syndrome approach argue that the term spectrum suggests a singular disorder with clinical symptoms varying within a given phenotypic range or spectrum. As a

syndrome, researchers such as Mary Coleman and Christopher Gillberg suggest that autism is a singular phenotypic presentation of different diseases with varying etiologies [172]. This approach suggests that autism may be a phenotype manifested as a result of different diseases and etiologies acting singularly or synergistically to produce the behavioral symptoms manifested clinically. Although Coleman's and Gillberg's suggestions differ from current norms within the ASD community, they do acknowledge the diagnostic importance of investigating autism as a spectrum disorder as it is necessary in the initial diagnosis. It is for the investigation of etiologies and the provision of therapeutics that these authors propose newer approaches, as the treatment of autism as a product of its etiology may be advantageous in providing more patient-tailored treatments. Whether a syndrome or a spectrum, it is evident that autism or ASD is the result of several etiologies. It is also evident that environmental triggers, when coupled with genetic polymorphisms, may lead to diverse phenotypic presentations. What is not known is how these factors, genetics and environment, interact in a given individual to precipitate this disorder.

These are just a few of the questions facing researchers today, and although significant advancements have been made, these advancements have also created more questions. Nevertheless, the identification of IL-6, among other discoveries, has paved the way for improved diagnostic criteria in addition to new therapeutic intervention points. The potential for IL-6 as an intervention point is also promising as it provides a measurable diagnostic marker in addition to potential therapeutic target. With these advancements, early therapeutic intervention, with the goal of significantly attenuating or alleviating the symptoms of ASD, may eventually become a treatment option as opposed to strictly palliative therapy.

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