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Prenatal stress and maternal immune dysregulation in autism spectrum disorders- potential points for intervention

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Abstract

Genetics are a major etiological contributor to autism spectrum disorder (ASD). Environmental factors, however, also appear to contribute. ASD pathophysiology due to gene x environment is also beginning to be explored. One reason to focus on environmental factors is that they may allow opportunities for intervention or prevention. Two such factors that have been associated with a significant proportion of ASD risk are prenatal stress exposure and maternal immune dysregulation. Maternal stress susceptibility appears to interact with prenatal stress exposure to affect offspring neurodevelopment. Additionally, understanding of the impact of maternal immune dysfunction on ASD has recently been advanced by recognition of specific fetal brain proteins targeted by maternal autoantibodies, and identification of unique mid-gestational maternal immune profiles. Animal models have been developed to explore pathophysiology targeting both of these factors. We are beginning to understand the behavioral, pharmacopathological, and epigenetic effects related to these interactions, as well as potential mitigating factors. Continued growth in understanding of these mechanisms may ultimately allow for the identification of multiple potential points for prevention or intervention for this subset of environmental-associated ASD cases.

Keywords

Autism spectrum disorder; prenatal stress; immune dysregulation; maternal antibodies; microbiome

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CONFLICTS OF INTEREST

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INTRODUCTION

While genetics is well-established as a leading contributor to the etiology of autism spectrum disorder (ASD) [1], the importance of non-genetic risk factors is increasingly recognized [2], with heritability estimated at 0.83 by the latest, more conservative, analysis [3], and 0.808 in a recent five country cohort [4]. While considerable research has explored the mechanism of action underlying specific genetic etiologies of ASD, environmental risk factors are less understood. The developmental origins of health and disease (DOHaD) theory proposes that the environment experienced during development *in utero* influences health after birth [5], including effects salient to ASD. Furthermore, genetics can critically interact with these influences, yielding gene x environment interactions (GxE) of importance for pathophysiology. Understanding the mechanisms of environmental risk may allow for possible prevention or reduced outcome severity, at least in a subset of ASD cases with known genetic risk factors, where the biological effects of environmental exposure can be enhanced due to genetic risk [6].

Several environmental factors that may occur during the prenatal period are associated with increased incidence of ASD. Two broad categories of factors with links to ASD risk are environmental exposures and maternal physiological states.

Maternal exposure to pollutants has consistently been associated with an increased risk, particularly for maternal exposure to air pollutants [7–10], with evidence of an interaction between air pollutant exposure and polymorphisms of the tyrosine kinase MET receptor gene [7]. Increased risk of ASD has also been associated with exposure to medication use in pregnancy, most notably for valproic acid [11]. Previous research has also reported an increased risk of ASD in association with prenatal exposure to β2-adrenergic agonists, commonly used to arrest premature labor, with an interaction between drug exposure and maternal polymorphisms in the β2-adrenergic receptor [12]. Other risk factors are being explored and identified including pesticides, endocrine disrupting chemicals, such as phthalates and bisphenol A, and maternal dietary factors, including a lack of folate supplementation during early pregnancy [13–15]. Increased parental age and short intervals between pregnancies have also been associated with increased risk of ASD [16,17]. Other studies have found no specific association with ASD, such as exposure to heavy metals [18].

Two prominent maternal psychophysiological risk factors repeatedly shown to be associated with the development of ASD are maternal stress exposure during gestation [19–21] and maternal immune dysfunction [22,23]. Elucidating the mechanism of action of these factors may allow multiple points for intervention or prevention.

PRENATAL STRESS

Psychological stress during pregnancy is known to affect behavioral and developmental outcomes in humans in general [24]. Early personality development in children, schizophrenia risk, and emotional disturbances are all impacted by maternal stress [25–28]. Relationships between maternal stress and offspring abnormal fear and anxiety-relevant responses as well as abnormal physiological stress reactivity have been observed persisting

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into adulthood in animal models [29,30]. The extent of this risk for ASD has been explored in a number of settings [6]. Initial evidence stemmed from surveys completed by mothers of children with ASD, Down syndrome, and neurotypical controls regarding the history and timing of prenatal psychosocial stressors that revealed a higher overall incidence of stressors among mothers of children with ASD compared to other groups. A peak was observed in reported stressors among mothers of children with ASD specifically at 25–28 weeks of gestation, which was not observed in the other groups [20]. Another independent group subsequently found a relationship between the occurrence and severity of tropical storms in Louisiana with specificity to a similar gestational timeframe, during the 5th-6th months of gestation, in association with the incidence of ASD births [21]. Further, prenatal maternal stress after a major Quebec ice storm was also found to be predictive of ASD traits in offspring [31]. Finally, a recent study reported that children with ASD exposed to prenatal stress may in general represent a more severe group than those with no history of prenatal stress exposure [32].

Larger epidemiological studies also support the relationship between prenatal stress and ASD [6]. Although a large Danish national registry study reported no association between maternal bereavement and ASD [33], an association was observed between maternal bereavement and ASD in this study prior to accounting for covariates such as maternal psychiatric conditions [33]. Other reports examining data from a Danish national registry study found that maternal psychiatric conditions were one of the strongest prenatal risk factors for ASD [34]. Reports examining data from a Swedish registry study also revealed a relationship between 3rd trimester maternal stress exposure and risk of ASD [35]. Furthermore, reports examining data from the Nurses' Health Study revealed that maternal exposure to partner abuse during pregnancy is strongly associated with ASD, although the timing of exposure with the strongest association with ASD was found to be earlier in gestation [19]. A recent meta-analysis has supported the association between prenatal maternal stress and risk of ASD [36].

Stress susceptibility

In each of these studies, a significant proportion of stress-exposed mothers had unaffected children. To understand why prenatal stressors might contribute to ASD only in some cases, GxE models are of particular interest. In GxE models, the effect of stress exposure is more salient in a subset of the population due to genetic risk.

For maternal stress exposure and its relationship to ASD, the serotonin transporter (SERT) gene is of particular interest because of its well-studied role in stress reactivity. The SERT gene encodes for the SERT protein, which transports extracellular serotonin back into the neuron [37]. Genetic variations in this gene can alter aspects of its function, such as protein expression and serotonin uptake [38–40]. The most widely studied variation is an insertion or deletion of a 43 base-pair segment of DNA within the promoter region of the SERT gene, *SLC6A4*, resulting in a long (L), rather than a short (S) allele [37–39]. Presence of the S-allele has also been linked to suicidality [41], greater cognitive flexibility impairment after stress exposure [42], increased susceptibility to anxiety [39], as well as greater activation of

the amygdala, the brain region critical for fear reactions [43] and altered in its function in ASD [44].

This gene also has relevance to ASD outside the setting of stress. Rigid-compulsive behaviors in ASD patients have also been associated with the region of the genome containing SERT in linkage studies [45]. A variation in a single nucleotide on the SERT gene, Gly56Ala, is additionally linked to increased risk of ASD [40]. An additional variant, the Ile425Leu variant, displayed a segregation pattern suggestive of male-biased linkage [46]. Furthermore, the S-allele of the SERT gene has been linked to ASD in some, but not all, studies [47–50].

In a mouse model, offspring of the dams that lacked a SERT gene and were exposed to prenatal stress had decreased social interaction as assessed by social approach and social novelty seeking with the 3-chamber social approach test [51]. The potential clinical salience of this model has been explored. Two independent sample populations of mothers were examined for both the presence of the S-allele as a genetic marker and for the presence of prenatal stress on stress surveys [52]. In both of the independent samples, it was found that the presence of the S-allele and the history of prenatal stress significantly co-segregated in mothers of children with ASD when stress occurred in the later critical period of pregnancy suggested in previous work [20,21,35]. Furthermore, there was no increased report of prenatal stress exposure, regardless of genotype, from these same mothers when queried about pregnancies of unaffected siblings, suggesting that the risk of the S-allele is not an overall increase in maternal recall of stress during pregnancy.

While observation of a specific GxE interaction for one candidate gene provides some insight, a wide variety of genes can interact with the stress response, including a range of other variants that affect SERT function [53]. Understanding general mechanisms by which the physiological effects of stress might act on the developing brain are necessary to move towards potential intervention efforts, and analysis of stress-associated or other genes may reveal molecular mechanisms contributing to an increased risk of ASD in association with prenatal stress. G x E interactions for prenatal stress exposure has received significant recent interest for neuropsychiatric conditions in general [54]. Examining the effect of these broader pathways on downstream neurobiological systems is important for understanding potential avenues of intervention.

One such system downstream of stress pathways is GABAergic inhibitory neuronal circuitry [54]. Significant abnormalities in the GABAergic system have been found in ASD [55,56], including expression of the GABA-producing enzyme, GAD67, which is reduced in post-mortem brains of individuals with ASD [57,58]. Magnetic resonance spectroscopy has shown reduced concentrations of GABA in auditory and motor brain regions and in the frontal cortex *in vivo* in patients with ASD [59–61]. Prenatal stress has additionally been shown to alter GABAergic neuronal migration and later GABAergic development [56,62,63]. Recent evidence also suggests that prenatal stress effects on other GABAergic progenitor processes, most significantly in striatum, and are most prominent in male offspring [64]. Thus, effects of prenatal stress on the GABAergic system are of interest for ASD.

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Prenatal stress and epigenetics

Another potential set of mechanisms by which prenatal stress exposure might impact offspring development includes epigenetic mechanisms. MicroRNAs (miRNAs), small RNA molecules that do not code for proteins, are gene regulatory mechanisms that can be influenced by environmental factors such as stress. Identifying alterations in miRNA after prenatal stress associated with ASD may help narrow the existing gap in our understanding of the mechanisms of GxE in ASD. For example, miRNAs in neonatal offspring brains can be modified by hemizygous deletion of a key placental gene that responds to stress in males only, O-GlcNAc transferase (OGT). OGT is one of a number of placental factors that respond to maternal stress in a sex-specific way, including peroxisome proliferator-activated receptors α (PPARα), insulin-like growth factor-binding protein 1 (IGFBP-1), GLUT4, and HIF3α [65,66]. These prenatal sex differences that influence developmental miRNA in the brain are of particular interest given the higher percentage of males with ASD.

miRNAs play a significant regulatory role in serotonergic pathways [67,68] and immune regulation [69], and are affected by prenatal stress in general [70–72]. In the G x E mouse model encompassing the heterozygous SERT knockout and prenatal stress, gene expression and miRNA changes induced by prenatal stress in offspring brains were greatly attenuated by maternal heterozygous SERT knockout genotype, in contrast to the robust changes observed in offspring brains after prenatal stress exposure in wild type pregnant dams [73]. This attenuation of gene expression and miRNA changes was associated with genome hypermethylation [73] (increased methyl groups bound to specific sites on the gene that affect the expression of that portion of DNA) which appeared to occur only through combined gene and environmental effects. Dysregulation of miR-103, miR-145, miR-219, miR-323, and miR-98 in offspring brain was found due to maternal stress exposure in rats [74], factors that may regulate neuroinflammatory responses and developmental pathways in brain. Additionally, other miRNAs are found to be associated with the stress response. For example, miR-135 regulates response to chronic stress through interaction with serotonergic activity [75], which may relate to the mechanisms contributing to ASD risk. MiR-155 is critical in immunity and inflammation [69]. Lastly, the role of specific miRNAs has been reported in regulating serotonergic genes (Let-7a) [67] and SERT (miR-16 & miR-15a) [76,77] as well as SLC6A4 (miR-325) [78].

Numerous epigenetic markers are also differentially expressed in ASD [79,80], with several involving critical components of the immune system detectable in blood [81]. As diffusible factors in blood are a central route by which maternal stress effects are communicated to offspring, it will be important to determine whether prenatal stress induced expression and methylation changes reported in animals [73] are also observed in maternal blood in prenatal stress-associated ASD cases. Furthermore, GABAergic changes observed in ASD [55,56], and the effects of prenatal stress on GABA systems as well as striatal dopamine [62,82], emphasize the importance of epigenetic changes on genes, such as changes on GABAergic genes related to behavioral deficits [83], which may be correctable by psychopharmacology after prenatal stress in mouse models. Such work may be fruitful for establishing biomarkers to monitor responsiveness, as novel therapeutic approaches are developed targeting these mechanisms. Lastly, Bale and colleagues have shown that epigenetic changes with prenatal

stress may be transgenerational [84]. Clinical implications of this transgenerational effect for ASD are unknown, as are the intriguing findings from animal models demonstrating effects of paternal stress exposure mediated by miRNA [85,86]. Additionally, animal model data suggests that preconceptual stress might impact a range of autism-associated behaviors in animal models, particularly in males [87], and in human populations, maternal exposure to childhood abuse has been associated with ASD [88], effects which also are likely mediated epigenetically [89].

Prenatal stress and the microbiome

Another critical factor that may play a role in the mechanism of prenatal stress is the microbiome. Significant attention has recently been drawn to the potential roles of the microbiome in neurodevelopment in general. The central nervous system (CNS) and the enteric nervous system (ENS) have long been known to have a bidirectional interaction, with implications for neurological disorders [90–92]. Recent evidence has suggested the importance of the gut microbiome in these relationships, and its specific importance in behavior [93–95], ENS and CNS neurodevelopment [94–96], CNS disorders [97], and cognitive development [98]. In animal models, the gut microbiome has been demonstrated to affect myelination [99,100] and associations between specific microbial profiles and CNS myelination have also been observed in human samples [101]. Gut microbiome composition has also been associated with differences in temperament in human infants, with some of the relationships observed to be stronger in males [102].

Maternal stress and microbial transmission together play an important role in early life programming and neurodevelopment [103]. Maternal prenatal stress is also known to affect infant intestinal micribiome as well as infant gastrointestinal problems in humans [104], and maternal anxiety also affects maternal microbial composition during pregnancy in humans [105]. In addition, maternal gut microbiota anomalies and/or maternal immune activation induce similar neurodevelopmental abnormalities in mouse offspring [106]. The microbiome has also been shown to be involved in immune regulation of the maternal immune activation (MIA) model of ASD [107]. The MIA model, in which mice are exposed to administration of polyinosinic:polycytidylic acid (poly I:C) models viral infection and results in progeny with ASD-associated abnormalities in behavior and CNS neurodevelopment as well as differences in the intestinal microbiome and intestinal permeability [93]. In one such model, investigators noted a dysbiosis in the stool of MIA progeny mice, particularly in the classes Clostridia and Bacteroides. Interestingly, treating the dysbiosis in these mice with *Bacteroides fragilis* corrected both the gastrointestinal (GI) permeability defects and ASD-related behavioral abnormalities [93]. These findings converge with human studies that demonstrate that *in utero* exposure to fever or infection, particularly of viral origin, are prominent risk factors for ASD [108–111]. As described below, immune system impairment has also been noted in both mothers of ASD patients and in ASD patients themselves [112].

The microbiome may be impacted by environmental risk factors other than in utero fever or infection. One recent study explored the mechanism underlying the connection between maternal obesity and increased ASD risk [113]. The investigators in this study demonstrated that the pups derived from a maternal obesity diet-induced model had a microbial dysbiosis

that was reversed with microbial reconstitution with *Lactobacillus reuteri*. Interestingly, these microbial changes were also correlated with normalized oxytocin levels in the CNS and reversal of abnormalities in synaptic potentiation in the ventral tegmental area [114], suggesting that the microbiome may have direct effects on brain signaling in this model.

The microbiome may also play a role in influencing the development or enhancement of comorbidities associated with ASD. For example, there may be a relationship between the microbiome and GI function in these individuals. GI dysfunction is over four-fold more common in children with ASD compared to neurotypical controls [115]. In the first multi-omic study of its kind in ASD, specific microbiome and immune profiles were found to be associated with comorbid gastrointestinal problems and abdominal pain [116]. Anxiety and stress reactivity also commonly co-occur in individuals with ASD, which may influence the microbiome [117] and stress reactivity is associated with GI disturbances in ASD [118]. Further, targeting the microbiome can reverse the impact of chronic stress in mice [119] and has anti-inflammatory effects in the CNS by attenuating stress-induced microglial changes and anxiety-like behavior [120]. In this way, the microbiome may be both a biomarker for and a route for therapeutic targeting of anxiety and stress-reactivity for individuals with ASD. The higher rates of ASD in males may also relate to sex-specific effects of the microbiome on the hippocampal serotonergic system [121], which is critically involved in stress responses.

Based on these interactions between the microbiome, immunity, neurodevelopment and social and affective behaviors [122], the role of the microbiome has received considerable attention for its potential importance in ASD [123–127]. Although there is currently no distinct microbial profile characteristic of ASD or a specific profile that is associated with its neurobehavioral manifestations, clinical trials examining the effects of probiotics and/or fecal microbial transplant on ASD have ensued. Mice administered *Lactobacillus reuteri* demonstrate improvements in GI and behavioral manifestations in ASD-associated behavioral models associated with environmental exposures including infection and maternal obesity [114,128]. Additionally, administration of *Lactobacillus reuteri* was found to rescue social deficits in other genetic, environmental, and idiopathic ASD models, which, interestingly, did not appear to be mediated by restoration of the host's gut microbiome, which remained altered in these models, and instead appearing to interact in a vagal nerve-dependent manner [129]. Further, pilot studies in humans indicated that a probiotic mixture of Lactobacilli and Bifidobacteria can improve GI symptoms and the quality of life in ASD patients [130]. The first fecal transplant study in individuals with ASD had excellent GI and behavioral outcomes. The study, however, was small and open-label [131] and did not address additional questions about immune profiles in ASD that might be secondarily impacted. It has recently been reported, however, that the benefits for gastrointestinal symptoms and autism-related symptoms, and increases in microbial diversity, appeared to be retained two years after the completion of treatment [132], again limited by the possibility of placebo affects in the open-label setting, with the lack of a control group to monitor change over time in untreated individuals, and the small sample.

Gut microbiome studies thus far have been small, utilized very different methodological analyses, and evaluated distinct patient populations [133]. Although these may be reasons

why microbial biomarkers have not yet been identified, another possibility is the large heterogeneity of ASD phenotypes [134] including the contributions of prenatal exposures across phenotypes. Highlighting the underlying mechanisms by which ASD phenotypes are guided by the developmental impact of the enteric microbiome on the central and enteric nervous systems may thus further of our understanding of ASD, and may bring us closer to the development of novel therapeutics.

Potential points of intervention for prenatal stress exposure

Certainly, efforts to mitigate the psychological effects of stress during pregnancy would seem prudent to minimize the impact on the developing offspring (see Figure 1). Of course, the risk vs benefit of pharmacological interventions for stress mitigation during pregnancy are unclear. Interventions targeting the microbiome and epigenetic mechanisms would also be of significant interest in this setting. However, intriguing evidence does suggest one low risk intervention.

In addition to the aforementioned GABAergic changes observed with exposure to prenatal stress, recent evidence has also revealed that prenatal stress-exposed mice from dams with heterozygous KO of SERT have significantly increased striatal dopamine [82]. It will be of future interest to determine whether ASD patients exposed to prenatal stress also represent a subgroup with significant striatal changes. Notably, administration of 1% docosahexaenoic acid (DHA) omega-3 fatty acid throughout pregnancy in dams, continuing the diet given to pups, reversed repetitive grooming behaviors, social interaction abnormalities, and altered striatal dopamine in mice exposed to prenatal stress born from dams with only one copy of the SERT gene, as compared to offspring that were untreated with DHA or only given DHA after birth [82]. While the clinical implications of this are as of yet unknown, DHA has been of particular interest due to its effects on a range of other neurological conditions due to its effects on a range of anti-oxidant pathways [135], and some evidence suggests synergistic effects with other anti-oxidant agents [136]. Additionally, redox dysregulation and maternal antioxidants may significantly impact offspring GABAergic system development [137]. Effects of DHA on redox regulation, the GABAergic system and on epigenetics in this setting are as of this time unknown. However, DHA has the advantage of being widely used, safely, during pregnancy. Furthermore, recent evidence suggests that combination with other biobotanicals, such as quercetin, can significantly lower the dose of DHA required to have a given level of antioxidant effect [136]. Finally, changes in the western diet across time to include a greater pro-inflammatory diet and a lower proportion of omega-3 fatty acids [138] might be relevant, and research might be warranted to determine whether a diet characterized by greater anti-inflammatory effects might serve to be protective against the impact of prenatal stress on offspring.

PRENATAL IMMUNE DYSREGULATION

Under normal conditions, the maternal immune system maintains a pathogen-free and non-inflammatory environment for the developing fetus [139,140]. Disruption of immune factors including cytokines, chemokines, and autoimmune sequelae including the production of autoantibodies during gestation can have adverse developmental consequences for the fetus.

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Epidemiological research has consistently found maternal fever or infection (viral, bacterial, and parasitic) during the first and/or second trimester are associated with increased risk of neurodevelopmental disorders (NDD), including ASD [141–146]. Further, using data from a large multi-site study, it was noted that women who had an infection during the second trimester of pregnancy accompanied by a fever were more likely to have children with ASD [147]. Thus, the above findings suggest that only more severe infections accompanied by a robust inflammatory response increase the risk of ASD in the child, and this phenomenon is not dependent on the pathogen itself, but rather the maternal response to the pathogen.

The maternal immune response to pathogens is largely driven by cytokines, which are signaling molecules produced by immune and other cells in response to infectious stimuli. In addition to directing the expansion or suppression of immune cells, the production of cytotoxic factors, and the production of antibodies, cytokines also mediate signals between the immune and nervous systems. This interaction can impact neuronal development and pruning, thereby shaping the developing brain. Cytokines and chemokines are involved in numerous aspects of typical neurodevelopment, including proliferation and differentiation of neural and glial cells, neuronal migration, dendritic branching, and synapse formation [148,149]. Some maternal cytokines may cross the placenta during gestation, as in the case of IL-6 [150–152], or act on placental cells to stimulate the downstream production of immune and other mediators in the fetal compartment [153]. The placenta of males has shown greater fluctuations in cytokine profiles and other changes after prenatal stress [84].

Fluctuations in the maternal levels of cytokines and chemokines can alter normal neurodevelopmental trajectories, potentially resulting in altered brain morphology and behavior in the offspring. Results derived from epidemiological studies utilizing mid-gestational maternal samples have further strengthened the notion that cytokine and chemokine dysregulation contributes to altered neurodevelopment relevant to ASD in offspring. Archived maternal serum from routine prenatal testing at 15–19 weeks of pregnancy was assessed in the Early Markers for Autism (EMA) Study, (a nested case-control prospective study) in order to investigate the relationship between mid-gestational maternal cytokines and chemokines and the risk of having a child with ASD or DD. In the pilot EMA study, increased maternal levels of circulating IFNγ, IL-4, and IL-5 at 15 to 19 weeks of gestation have been reported in mothers of children with ASD as compared to mothers of general population (GP) control children [154]. In addition, increased mid-gestational levels of IL-2, IL-4, and IL-6 were found in mothers of children with developmental delay (DD) compared to the mothers of GP controls [154], suggesting that unique mid-gestational cytokine profiles might influence specific neurodevelopmental processes and result in different types of NDDs. In the subsequent larger EMA study, levels of 22 cytokines and chemokines were measured on an independent sample of 1,031 mid-gestational maternal specimens. Significant elevation in the mid-gestational levels of several pro-inflammatory cytokines and chemokines was found to be distinctly associated with an increased risk of having a child with ASD with intellectual disability (ASD+ID) compared to both GP and DD groups [155]. This larger study enabled the differentiation between ASD sub-phenotypes and suggests that mothers of children with ASD and ID have significantly elevated mid-gestational levels of inflammatory cytokines/chemokines compared to all other groups examined. The immunologic distinction between mothers of children with ASD and

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ID and those with ASD without ID or DD without ASD suggests that the ID associated with ASD might be etiologically distinct from DD without ASD [155]. Studies thus far have primarily been cross-sectional, with limited assessment of the relative importance of different stages of pregnancy or of differential effects in males and females. Based on studies of gestational cytokine profiles during a typical pregnancy [156,157], greater differences could be induced in cytokines between the 1st and 2nd trimesters, prior to the development of the maximal cellular immune regulation needed to avoid fetal rejection.

Animal models have provided additional evidence that specific maternal immune factor changes, including those observed in maternal immune activation, can affect behavior and neuromorphology in offspring [158–162]. These immune-mediated effects have been employed to model several neurodevelopmental disorders, including schizophrenia [163–165], cerebral palsy [166], and ASD [167,168]. Additionally, the effects of maternal immune activation have been demonstrated to be long-lasting on offspring brain development and behavior [159,169,170]. Such studies also provide the opportunity to explore the mechanisms by which maternal immune factors alter the neurodevelopmental trajectory. A striking example of these principles involves maternal autoantibodies reactive towards fetal brain proteins which have been observed in a significant number of mothers of children with ASD while only rarely being detected in mothers of unaffected children [171–173]. Maternal IgG antibodies readily cross the placenta during pregnancy in humans to equip the immunologically naïve fetus with antibodies to protect against infectious agents. These maternal IgG antibodies persist up to six months postnatally [174]. Along with IgG antibodies that are immunoprotective, however, autoantibodies that react to fetal ‘self’-proteins are also able to cross the placenta. Several neonatal autoimmune diseases are known to result from this transfer of pathogenic maternal IgG [175–177] and reports are suggestive of a similar role of these autoantibodies in ASD [178–181]. Additional studies have confirmed that these autoantibodies are present in mothers for up to 18 years following the birth of an affected child [182]. Polymorphisms of the MET gene appears to relate to the maternal production of these autoantibodies [183]. Furthermore, these IgG maternal autoantibodies, when derived from human samples and incorporated into animal models, have been demonstrated to produce ASD-relevant behaviors [184]. In a non-human primate study, IgG isolated from mothers of children with ASD was administered intravenously to rhesus monkey dams during gestation, resulting in notable whole-body stereotypies and increased motor activity at 15 months [185]. The specific autoantibodies involved have been recently identified as the fetal brain proteins lactate dehydrogenase A and B (LDH-A, LDH-B), collapsin response mediator proteins 1 and 2 (CRMP1, CRMP2), Y-box binding protein 1 (YBX1), stress-induced phosphoprotein 1 (STIP1), and guanine deaminase (GDA) [172]. In this initial discovery study, maternal reactivity to particular combinations of these autoantigens is significantly associated with an outcome of ASD in the child. When all autoantigen reactivity patterns were combined, a total of ~20% of mothers of children with ASD had one of the autoantibody patterns containing two or more of the target autoantigenic proteins relative to <1% of control mothers. Non-human primate studies using passive transfer of human IgG reactive to the LDH, CRMP1, STIP1 ASD-specific pattern have also demonstrated that antibody profiles in ASD may be related to early neurodevelopmental alterations, as well as brain overgrowth in exposed offspring, a finding that was specific to

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males [186]. Further, an LDH, CRMP1, STIP1 antigen-driven endogenous mouse model of maternal autoantibody related (MAR) ASD has recently demonstrated that prenatal exposure to these ASD-specific maternal autoantibodies resulted in ASD-relevant alterations to behavior and neuroanatomical measures in prenatally exposed offspring for both males and females [23]. Immune alterations in the brain, including neuroglial (i.e. microglial) activation and CNS inflammation [187,188] have been noted in individuals with ASD. Furthermore, circulating antibodies reactive to neuronal tissue have been observed in children with ASD [171,181,189–193]. These studies suggest that immune dysregulation in the ASD child is also of potential significance. At this time, we do not have recognized treatment options for either the prenatal inflammatory sequelae or for the mitigation of the maternal autoantibody response.

As stress can have a notable impact on immune function [138], and maternal immune challenges such as infection during pregnancy increase ASD risk [145], the roles of brain-reactive autoantibodies and other immune molecules are of significant interest for understanding prenatal exposure more broadly. In many settings, chronic stress is considered an immunosuppressant. However, the immunosuppressant effects of stress can cause paradoxical pro-inflammatory reactions by reactivation of latent viruses [194] and acute stress responses may be pro-inflammatory [195]. Prenatal stress effects on microglia in mouse offspring have been shown to involve maternal IL-6 signaling [196]. Prenatal stress has been demonstrated to increase cord-blood IgE levels [197] and, in a non-human primate model, may influence maternal transfer of IgG to offspring in a sex-dependent manner [198]. Furthermore, recent evidence revealed strong relationships between SERT function, previously discussed as important in stress regulation, and the immune response, including SERT expression in B-cells responsible for antibody production [199]. With these known interactions between stress, serotonin, and immunity, it will be of interest to see how these and other stress-related factors interact in clinical populations at risk for ASD.

Potential points of intervention for prenatal immune dysregulation

If it is indeed revealed that prenatal stress and maternal immunity are related, interventions targeting prenatal stress exposure might also have an impact on maternal immunity (see Figure 1). Furthermore, mitigation of inflammation during pregnancy may also affect systems related to the stress response. As we come to better understand the relationship between stress, immune dysregulation and neurodevelopment, we will be better able to construct targeted interventions to reduce the impact on neurodevelopmental outcome. In general, given that downstream disruptions arising from prenatal stress and maternal immunity in the offspring may be the same, interventions to correct previously induced changes at the level of the offspring or through maternal intervention during the critical lactation period may be effective. Recent evidence has revealed that exercise reverses the behavioral and synaptic abnormalities that arise after maternal inflammation [200], raising the possibility of exercise interventions for other types of maternal immune dysregulation, and perhaps the possibility from other interventions that might target similar mechanisms. Finally, as with prenatal stress, and given the relationship between pro-inflammatory diets and microbiome [201], and the increase in the pro-inflammatory effects of the western diet across recent history [138], research might be warranted to determine whether a diet with

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greater anti-inflammatory content might also serve to be protective against the effects of maternal immune dysregulation on offspring.

CONCLUSIONS

While genetic factors are a major contributor to the etiology of ASD, mounting evidence supports a role for environmental factors, allowing possibilities for prevention or early intervention. Prenatal stress and maternal immune dysfunction appear to contribute in some way to a significant proportion of these ASD cases. Efforts towards gaining a better understanding of how these factors interact with genetic susceptibility, particularly in mothers, will result in an increased ability to identify those individuals at greatest risk of developing ASD with such exposures. Furthermore, research aimed at gaining an understanding of downstream mechanisms will allow for the identification of multiple potential points for novel preventative measures and/or interventions (Figure 1). It will also be important to see if these factors result in common downstream mechanistic pathways with some of the genetic contributors to ASD, allowing for a more comprehensive approach for intervention in ASD based on personalized therapeutic approaches [202]. While interventions that target these mechanisms are as of yet unknown, evidence is beginning to suggest several intriguing possible approaches.

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ABBREVIATIONS

ASD	autism spectrum disorder
CNS	central nervous system
CRMP	collapsin response mediator proteins
DD	developmental delay
DHA	docosahexaenoic acid
DNA	deoxyribonucleic acid
DOHaD	developmental origins of health and disease
EMA	Early Markers for Autism
ENS	enteric nervous system
GABA	gamma amino butyric acid
GDA	guanine deaminase
GP	general population
GI	gastrointestinal

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GxE	gene x environment interactions
ID	intellectual disability
Ig	immunoglobulin
IGFBP-1	insulin-like growth factor-binding protein 1
KO	knockout
LDH	lactate dehydrogenase
L-allele	long allele
MAR	maternal autoantibody related
MIA	maternal immune activation
miRNA	MicroRNAs
NDD	neurodevelopmental disorders
OGT	O-GlcNAc transferase
poly I:C	polyinosinic:polycytidylic acid
PPARα	peroxisome proliferator-activated receptors α
RNA	ribonucleic acid
S-allele	short allele
SERT	serotonin transporter
STIP	stress-induced phosphoprotein
YBX	Y-box binding protein

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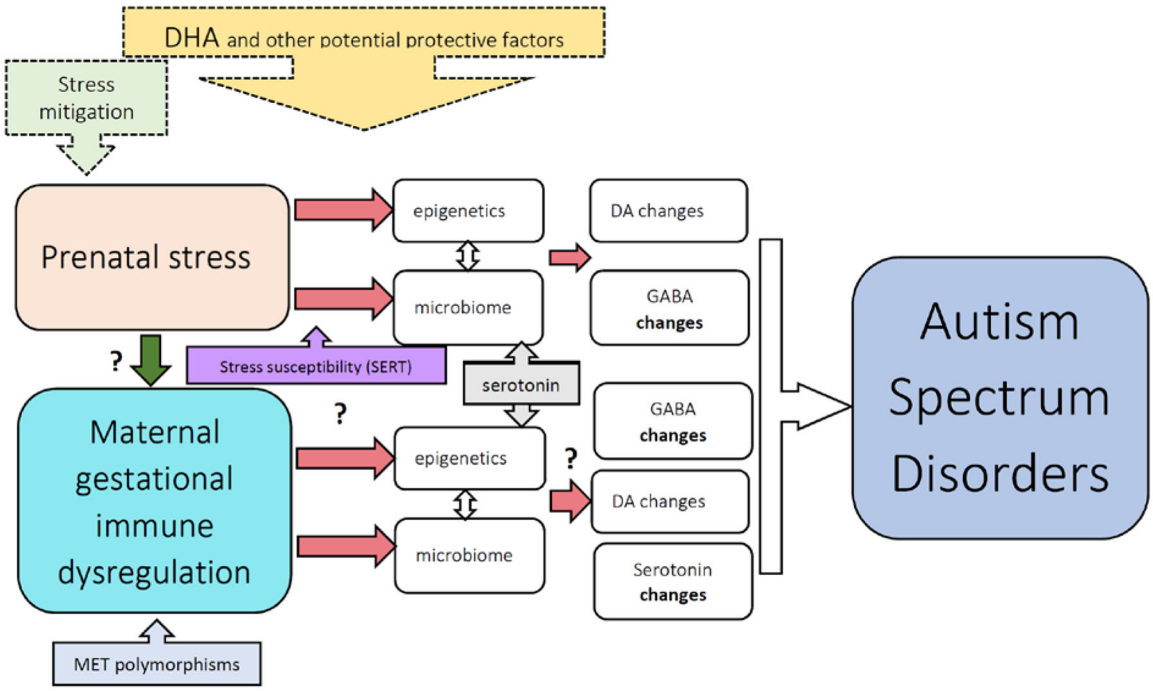

Figure 1.

Schematic of potential pathways of effects of prenatal stress exposure and maternal immune dysregulation on neurodevelopment relevant to ASD. Evidence suggests that the microbiome and epigenetic changes as described herein are involved with the mechanism of prenatal stress, with suspected downstream changes on neurotransmitter systems. The effects of prenatal stress can be enhanced by variations in maternal genetics impacting other neurotransmitter systems. The specific mechanisms are less established for maternal gestational immune dysregulation. While we know some of the effects of maternal autoantibodies on developmental pathways, we are less clear on the effects of maternal inflammation during gestation. Maternal immune dysregulation can also be impacted by genetics. Further, how to mitigate these effects is still under investigation. This figure designed more to be illustrative than comprehensive, suggests several potential points for intervention along these pathways. Efforts at stress mitigation would clearly act on the prenatal stress level, and DHA and other potential protective factors may act at a level afferent to the neurotransmitter effects.