Immune Involvement in Autism Spectrum Disorder as a Basis for Animal Models

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Abstract

Several of the environmental stimuli suggested to play a role in the pathogenesis of ASD involve altered immune responses during gestation. In this review, we discuss maternal immune activation as a primary risk factor for ASD, with an emphasis on recent findings from animal models of prenatal immune challenges. We further address the presence of autoantibodies as an additional immune-related autism risk factor, drawing upon work done in rodent and monkey models. We then explore the intersection between genetic and environmental susceptibility, with a focus on gene-environment interactions and immune involvement, in genetic risk factors for autism. Finally, we provide emerging evidence for the role of immune dysregulation in the pathogenesis of ASD.

Introduction

Autism spectrum disorder (ASD) consists of a heterogeneous group of syndromes, defined by the presence and severity of repetitive/stereotypic behaviors, abnormal social interaction and impaired communication. ASD is highly heritable, as indicated by increased concordance in monozygotic versus dizygotic twins, and by elevated risk observed in the siblings of an affected child [1]. Accordingly, genome-wide association and linkage studies have uncovered a number of genetic copy number variants, short nucleotide polymorphisms and common risk variants that increase the susceptibility for ASD [2]. Despite continued advances in next generation sequencing, very few ASD cases can be attributed to a defined genetic etiology, and it is estimated that identified genetic risk factors collectively account for only 10-20% of ASD cases [3,4]. Moreover, findings from two very large autism twin studies demonstrate a significant difference in concordance between dizygotic twins and non-twin siblings, indicating a substantial contribution of the maternal-fetal environment to ASD risk [1,5]. This, combined with profound increases in autism prevalence over the past two decades [6], highlights the importance of environmental factors in the etiology of ASD.

Immune-related risk factors for ASD

Maternal immune activation: Several environmental factors increase susceptibility to ASD, with early immune activation being one of the most strongly supported by epidemiological, clinical and animal studies [7]. Large epidemiological studies assessing over 10,000 ASD cases from Danish national birth records and over 4,000 ASD cases identified from Swedish residence registries, demonstrate that maternal infection during pregnancy increases the risk for ASD [8,9]. In addition, early infection with any of a variety of pathogens, including rubella, cytomegalovirus or varicella, is linked to elevated autism risk [7]. The impact of maternal immune activation (MIA) on ASD is further supported by associations between maternal fever during pregnancy and ASD [10]. Moreover, elevation of the cytokines IFN-γ, IL-4 and IL-5 in maternal blood, and TNFα and MCP-1 in amniotic fluid is linked to risk for ASD [11-14].

In animals, MIA is induced by perinatal infection with specific pathogens, exposure to Microbe-Associated Molecular Patterns (MAMPs) or direct administration of recombinant cytokines. MIA by any of these inflammatory stimuli leads to autism- and schizophrenia-related behavioral abnormalities in the offspring (reviewed in [15-18]). Intranasal inoculation of pregnant mice with influenza virus, for example,

yields offspring with heightened anxiety, deficient sensorimotor gating and reduced social interaction, and a localized reduction in Purkinje cell number [19], all features of autism. Moreover, offspring of mothers injected with the viral mimic poly(I:C) during midgestation, exhibit the three cardinal behavioral symptoms of autism: impaired sociability and social preference; defective communication as assessed by pup and adult ultrasonic vocalizations and odorant communication by scent marking; and elevated repetitive behaviors as measured by self-grooming and stereotyped marble burying [20,21]. Similar changes in core ASD-related behaviors are observed after first trimester injection of LPS in pregnant rats [22]. Midgestational injection of recombinant IL-6 in pregnant mice is sufficient to induce behavioral deficits in the offspring that are comparable to those induced by maternal influenza or poly (I:C) injection [23,24]. Similarly, maternal IL-2 injection leads to anxiety-like and repetitive behaviors in mouse offspring [25]. In contrast, over-expression of the anti-inflammatory cytokine IL-10 in pregnant mice sufficiently prevents MIA-induced behavioral, and biochemical abnormalities in the offspring [26]. In addition, several studies utilizing early postnatal immune activation in rodents, to better mimic second trimester human brain development, also report long-term changes in neuropathology and behavior [27,28].

The impact of MIA on brain and behavior is further supported by non-human primate studies. Pregnant rhesus monkeys infected with influenza virus during the third trimester yield offspring with significant decreases in cortical gray matter and reduced white matter in the parietal lobe, in addition to decreased social contact with the mother [29]. Notably, these abnormalities occur in the absence of primary viral infection of the fetal compartment. Low-dose maternal LPS injection in monkeys, however, leads to the opposite neural phenotype in which infant offspring display increased cortical white matter compared to controls, analogous to changes observed in autistic children, and

decreased vocalizations during an intruder paradigm, among several other behavioral abnormalities [30]. First or second trimester maternal poly(I:C) injection of rhesus macaques also leads to autism-related endophenotypes in the offspring, including motor stereotypies, elevated distress and self-soothing behaviors, and a deficit in verbalizations [31]. Overall, that MIA can be translated to non-human primate models to induce ASD-related neuropathology and behavioral symptoms, further supports the study of MIA in animals as models with face and construct validity for autism.

The symptomatic overlap between different modes of MIA indicates that the production of pro-inflammatory cytokines in response to immune activation is likely a key pathophysiological step in the development of autism-related impairments. It is well established that MIA induces a maternal pro-inflammatory response that is quickly relayed to the maternal-fetal interface. Several pro-inflammatory cytokines, including IL-6, IL-1β and TNFα, are elevated in the placenta and amniotic fluid, by onehour post MIA challenge [32-34]. Maternal LPS injection can lead to dramatic changes in placental physiology, including necrosis, infiltration of immune cells and altered perfusion [35,36]. Similar changes are observed in placentas from influenza-infected mothers, in addition to widespread effects on the placental transcriptome [37]. Furthermore, placentas from poly (I:C)- injected mothers exhibit increased activation of decidual immune cells and altered endocrine function [23]. Interestingly, placental trophoblast cells are activated in response to MIA, reflecting a direct transfer of the maternal MIA response to fetally-derived placental cells. It is very likely, however, that the extent of placental damage seen in these various models depends on the dose of the agent administered. Altogether, the downstream effects in the placenta raise the intriguing question of how changes at the maternal-fetal interface impact fetal brain development. Notably, subclassification of ASD cases by behavioral symptoms, patient and family history and biological endophenotypes reveals that immune dysregulation in autism and obstetric complications in the mother cluster together as central characteristics of a subgroup of ASD individuals [38]. Moreover, trophoblast inclusion histopathology is found in placentas from births that yield an ASD outcome [39]. Given that MIA can induce striking placental pathology, it seems likely that the maternal infection risk factor contributes to pre-term birth, low birth weight and obstetric complications, which are each associated with increased risk for ASD [40-43].

In addition to altering placental status, MIA quickly leads to altered gene expression and cytokine profiles in the fetal brain. Shortly after MIA, the fetal brain exhibits elevated levels of pro-inflammatory cytokines [44], suggesting a possible feed-forward propagation of pro-inflammatory MIA responses from the maternal circulation to the placenta, and to the fetus itself. The initial induction of fetal brain cytokines typically diminishes after 24 hours post MIA, but may trigger molecular events that lead to lasting neuroimmune changes. Consistent with this notion, poly (I:C) offspring exhibit dynamic age- and region-specific changes in brain cytokines throughout postnatal development [45,46]. In response to maternal LPS, fetal brains exhibit altered gene expression profiles, with upregulation of genes related to oxidative stress and down regulation of genes related to GABAergic interneuron migration [15]. After maternal influenza infection, embryos exhibit altered brain expression of many genes relevant to autism and schizophrenia, including *Sema3a*, *Foxp2* and *Vldlr* [47]. Furthermore, MIA induction by influenza, poly (I:C) or recombinant IL-6 injection, results in distinct as well as shared changes in gene expression in the embryonic brain. Of particular note is the upregulation of genes of the crystallin small heat shock protein family [48]. Interestingly, the

severity of these gene expression changes correlates with reductions in placental weight, suggesting that placental status can serve as a marker of disrupted neurodevelopment. This is consistent with findings that placental size correlates with the risk for several adult-onset diseases [49-52]. Acute transcriptional changes and cytokine effects in the fetal brain may serve as an underlying basis for several of the neurodevelopmental impairments observed in MIA offspring (reviewed in [15-18]), including altered cortical neurogenesis [53,54], hippocampal synaptic transmission [55,56] and serotonergic and dopaminergic signaling [57-59].

Research conducted in MIA animal models collectively demonstrate that transient immune activation is sufficient to cause long-term changes in neurodevelopment and behavior. However, the particular phenotypes induced by MIA differ depending on the type, timing, frequency and route of administration, as well as the genetic and immunological background of the host [26,34,60,61]. Such variations across MIA studies impede cross-comparison between findings [16]. At the same time, the information garnered from diverse MIA studies raises the intriguing question of whether differences in the severity, timing and type of MIA can produce distinct forms of neurodevelopmental disorders. The distinction between ASD and schizophrenia is particularly interesting in this regard, as the association between maternal infection and increased schizophrenia risk in the offspring, is supported by numerous epidemiological and clinical studies [7,62]. Moreover, schizophrenia and autism have several shared clinical features, including social withdrawal, impaired communication and deficient sensorimotor gating, as well as shared genetic susceptibility factors [63]. Offspring of immune activated dams exhibit features of both schizophrenia and autism, including decreased pre-pulse inhibition and social interactions, and elevated anxiety, leading to the use of MIA in animals to model both disorders [16,17]. It will be interesting to assess how particular autism- versus schizophrenia-related symptoms, are modulated by changes in timing, intensity and type of MIA [64]. It will also be important to test for endophenotypes that are not shared between these disorders such as repetitive/stereotyped behaviors [21], which are characteristic of autism, and enlarged ventricles [65] and enhanced sensitivity to hallucinogenic drugs [66], which are characteristic of schizophrenia.

The role of MIA has been explored in several recent gene x environment studies, supporting the interaction of both environmental influence and genetic susceptibility in the pathogenesis of neurodevelopmental disorders, such as autism and schizophrenia. In transgenic mice expressing mutant human DISC1, poly(I:C)-induced MIA interacts with genetic risk to alter social behavior and produce depression and enhance anxiety-like symptoms, along with several neurochemical and neuropathological changes, such as decreased number of hippocamal granule cell dendrites and reduced serotonergic neurotransmission [67]. MIA also synergizes with genetic *Nurr1* deficiency to exacerbate sensorimotor and attentional behavior, and to alter expression of dopaminergic markers in the prefrontal cortex and ventral striatum [68]. In a mouse model of tuberous sclerosis, maternal poly(I:C) injection and *Tsc2* haploinsufficiency together, lead to increased gestational miscarriage and abnormal social approach behavior [69]. Together, these studies support the importance of environmental risk factors, in predisposing for neurodevelopmental disease in individuals displaying genetic susceptibility.

Autoantibodies in ASD mothers or individuals: Another immune-mediated risk factor for ASD involves serum immunoglobulins that react against self-antigens. Such "autoantibodies" have been identified in plasma from mothers of ASD children and from ASD individuals themselves, and some have been shown to react against neural components, including myelin basic protein and GAD65 in cerebellar Purkinje cells [70-72]. Although the majority of these autoantibodies

are also detected at some frequency in non-ASD, typical controls, particular maternal autoantibodies that react against fetal brain proteins at approximately 37 kDa and 73 kDa display high specificity to autism cases, with striking reproducibility across large experimental cohorts [70]. Importantly, autoantibodies with the same reactivity have also been identified in plasma collected during the gestational period from ASD mothers, in contrast to typical studies that isolate the autoantibodies from samples collected up to 18 years post-partum [73]. Moreover, the autoantibodies are reported to correlate with impaired expressive language in ASD children [74]. Identifying the specific target antigens to which these autoantibodies react, will be critical in uncovering a mechanistic link between maternal autoantibodies and ASD. Furthermore, whether maternal autoantibodies can be detected in corresponding ASD children is unclear.
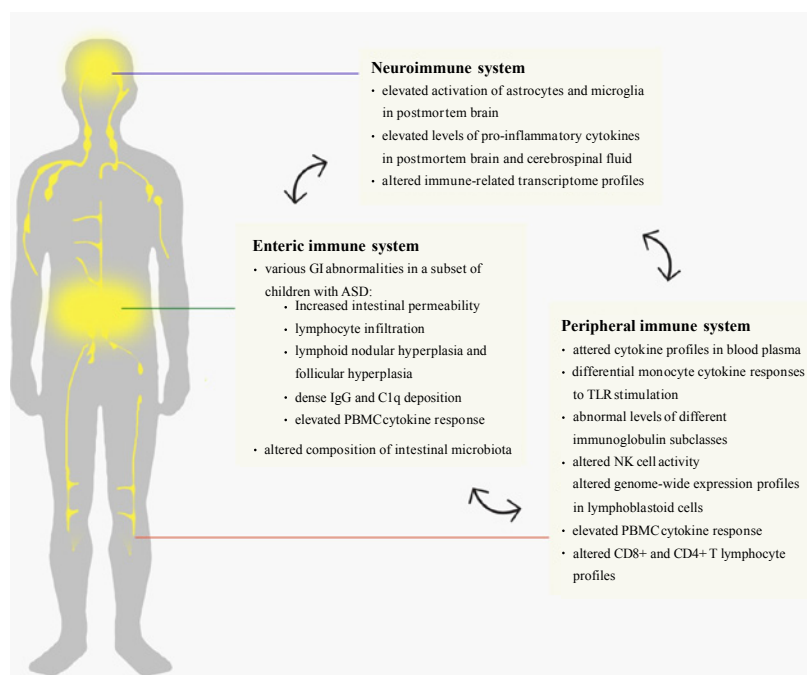
Studies that translate this autoantibody risk factor to animal models for ASD are intriguing, but few. An early case study identified anti-Purkinje cell antibodies in a mother of an ASD child [75]. Daily injection of this serum into pregnant mice from E10 to E17 yields offspring with decreased exploration and impaired motor coordination. In another study, injection of purified IgG pooled from over 60 ASD mothers into pregnant mice, resulted in heightened anxiety, hyperactivity and an age-specific deficit in sociability [76]. An additional study in rhesus macaques revealed that first-trimester injection of pregnant monkeys with IgG pooled from 21 ASD mothers yields offspring that display whole body stereotypies, hyperactivity and increased nonsocial behavior [77]. Lastly, a recent study involved injection of pregnant mice with ASD-specific immunoglobulins isolated from mothers of children with autism [78]. Strikingly, offspring of maternal ASD-related IgG exposure developed abnormal pup vocalizations, impaired sensory and motor coordination and increased anxiety-like behavior.

Much remains to be explored in animal models of the autoantibody risk factor for ASD, including the question of whether maternal autoantibodies can cross the placenta and enter the fetal brain at significant levels. And importantly, what are the antigenic targets of particular autoantibody subclasses, and are these antigens specific to the fetal brain? Interestingly, a study examining reactivity of different ASD-associated maternal autoantibodies to various tissues reveals that some react against proteins from adult brain and fetal small intestine. In such cases, it will be important to assess effects of ASD-related IgG on maternal behavior and physiology, and to determine whether reactivity of autoantibodies against non-CNS antigens represents an indirect effect of autoantibodies on brain and behavior. Notably, the impact of autoantibodies derived from ASD individuals, rather than their mothers, has not yet been evaluated in animal models. In addition, the cause of ASD-related autoantibody production has been largely unexplored. It will be fascinating to evaluate whether autoantibody production occurs as a result of other ASD-related genetic and environmental risk factors. Two models of particular interest are MIA, which displays evidence of disrupted immunological tolerance at the maternal-fetal interface [35,36], and MET-deficient mice, in light of findings linking a MET common risk variant to ASD-related autoantibodies in clinical cohorts [78]. Finally, autoantibody animal models will serve as a useful tool to explore potential therapeutics for treatment of autism, in well-defined subsets of ASD individuals.

Immune dysregulation in ASD

MIA and maternal autoantibody production represent two immune-mediated risk factors, whose influences during early life may contribute to ASD onset. In addition to these prenatal immune insults, increasing evidence highlights a role for postnatal immune alterations in the pathogenesis of ASD [79,80]. Several studies report striking immune dysregulation in the neural, peripheral and enteric immune systems, of autistic individuals (Figure 1). Postmortem brains from ASD patients exhibit elevated activation of microglia and astrocytes, in addition to increased levels of pro-inflammatory cytokines [81,82]. Notably, transcriptome analysis of ASD brains reveals altered

Neuroimmune system
· elevated activation of astrocytes and microglia in postmortem brain
· elevated levels of pro-inflammatory cytokines in postmortem brain and cerebrospinal fluid
· altered immune-related transcriptome profiles

Enteric immune system
· various GI abnormalities in a subset of children with ASD:
  · Increased intestinal permeability
  · lymphocyte infiltration
  · lymphoid nodular hyperplasia and follicular hyperplasia
  · dense IgG and C1q deposition
  · elevated PBMC cytokine response
· altered composition of intestinal microbiota

Peripheral immune system
· altered cytokine profiles in blood plasma
· differential monocyte cytokine responses to TLR stimulation
· abnormal levels of different immunoglobulin subclasses
· altered NK cell activity altered genome-wide expression profiles in lymphoblastoid cells
· elevated PBMC cytokine response
· altered CD8+ and CD4+ T lymphocyte profiles

Figure 1: Widespread immune dysregulation may play a role in ASD: Autistic individuals display a variety of immune abnormalities in the brain, periphery and gastrointestinal tract that may contribute to the pathogenesis or maintenance of ASD symptoms.

expression of neuronal-related genes, including ASD susceptibility genes, alongside dysregulated expression of immune-related genes related to inflammation and glial activation [79,83]. Altered cytokine profiles are also observed in cerebrospinal fluid and sera collected from living autistic individuals [81,82,84]. In the periphery, several subsets of leukocytes isolated from ASD blood display altered function, reflecting altered innate and adaptive immune responses [80]. Interestingly, significant subsets of autistic children experience gastrointestinal complications, including increased intestinal permeability, lymphoid hyperplasia, lymphocyte infiltration and altered microbial composition [85-87]. Importantly, a number of these autism-associated immune changes are associated with elevated severity of ASD symptoms [80].

Immune effects on behavioral symptoms of ASD: Whether immune abnormalities in the brain, periphery and/or gastrointestinal tract are involved in the development or persistence of ASD symptoms is unclear. However, it is well established that immune status across all of these domains is important for normal brain function and behavior. Cytokines in the brain play a fundamental role in synaptic development, and traditional components of the immune system, such as complement proteins and major histocompatibility complexes, are critical for synaptic pruning, neuronal plasticity and the patterning of neural circuits in the normal brain [88-92]. In the periphery, cytokine responses to infection are known to stimulate vagal nerve afferents, ultimately leading to altered behavior [93]. Furthermore, knockout of canonical immune components, such as RAG1 and T cell receptor, leads to impaired cognitive behavior, learning and memory [94-96]. In the gastrointestinal tract, the commensal microbiota plays a critical role in the development and status of the immune system [97]. Interestingly, germ-free animals reared in the absence of any microbial exposure exhibit abnormalities in nociceptive, emotional, motor and anxiety-like behaviors [98,99]. Overall, several lines of evidence suggest that immune alterations could directly contribute to the pathogenesis or maintenance of ASD symptoms.

Recent studies in animal models have explored the influence of systemic immune dysfunction on ASD symptoms. In addition to core ASD symptoms and neuropathology, poly(I:C) MIA offspring exhibit lasting peripheral immune dysregulation, including hyper-responsive CD4+ T cells and deficits in splenic regulatory T cells [32,33]. Poly(I:C) offspring also exhibit altered immune function in the mesenteric lymph nodes, as well as deficient intestinal barrier integrity, which is reminiscent of GI abnormalities seen in subsets of ASD individuals [32,100]. There is also evidence of microglial activation in some MIA models [101,102]. Recent experiments support the notion that systemic immune abnormalities can contribute to the persistence of ASD-related symptoms. Following irradiation and bone marrow transplantation, poly(I:C) offspring exhibit decreased stereotypic and anxiety-like behaviors [32]. Similar findings are observed in a mouse model of Rett syndrome, where irradiation and bone marrow transplantation in MeCP2 knockout mice arrests disease development as measured by lifespan, respiration, body weight and locomotion [103]. Importantly, however, the improvement observed in the Rett model is attributed to engraftment of new microglial cells, whereas the improvement observed in the MIA model is primarily an effect on peripheral immunity. In addition, the BTBR strain, which displays reduced sociability and verbal communication compared to several other mouse strains, also exhibits increased peripheral CD4+ T cells, peripheral B cells and serum and brain immunoglobulin levels, among other immune abnormalities [104]. The role of immune abnormalities on ASD symptoms in the BTBR mice, however, is unknown. Extending these types of studies to additional animal models for autism will be important for better defining the immune-ASD connection. The notion that immune abnormalities may arise as a result of genetic alterations is also interesting in light of the several ASD genes that are relevant to both brain and immune function, including those encoding various HLA haplotypes, receptor tyrosine kinase and complement C4B protein [105-108]. Unfortunately, few of these immune-related genetic risk factors for autism have been translated to animal models or evaluated for ASD-related immune and behavioral symptoms. Future studies in these areas will be important for identifying converging pathways for several related environmental and genetic risk factors for ASD.

Immune therapies for ASD

Despite numerous findings of immune abnormalities in autism and the known effects of immune modulation on brain and behavior, there are very few published, controlled studies evaluating the efficacy of immunomodulatory therapeutics in treating ASD symptoms [109]. Intravenous immunoglobulin treatment has been evaluated in ASD case studies, where up to 10-20% of children undergoing treatment exhibit symptomatic improvement [110]. Oral immunoglobulin treatment, however, has no significant effect on GI symptoms in ASD children [111]. Also interesting is that fever is associated with improved behavioral symptoms in ASD children [112]. The anti-inflammatory antibiotic minocycline can rescue synaptic abnormalities and deficits in ultrasonic vocalizations in mouse models of fragile X syndrome, and recent studies report efficacy in treating symptoms in fragile X patients [113-115]. Whether it is also effective in autism is still unclear, although a small pilot study reported no significant clinical improvement after treatment in ASD children [116]. The antibiotic D-cycloserine is effective in treating social impairments and stereotypic behavior in animal models relevant to autism [117,118], and has also reduced social withdrawal in a small clinical cohort of ASD children [119]. These effects are commonly attributed to the activity of D-cycloserine as a partial NMDA-receptor agonist, but whether its antibiotic properties are also important in this regard are unknown.

Several other classes of drugs that are used to treat ASD, including antidepressants and antipsychotics, are known to display immunomodulatory properties. The antipsychotic drug risperidone is FDA-approved for treatment of ASD symptoms, and also known to modulate immune function, T cell differentiation and serum cytokine profiles via suppression of the AKT/NFkB pathway [120-123]. The antidepressant aripiprazole has effectively treated irritability, hyperactivity and stereotypy in two large randomized controlled trials of ASD children [124], and is reported to prevent microglial activation, reduce reactive oxygen species and suppress pro-inflammatory cytokines [125]. Fluoxetine, another antidepressant, exhibits several effects on immune function [126-129] and has reduced repetitive behaviors in a double-blind placebo-controlled trial of adults with ASD [130]. The beneficial effects of the acetylcholinesterase inhibitors, galantamine and donepezil on reducing social withdrawal, irritability and inattention in children with autism [131,132] are believed to be due in part to activation of the cholinergic anti-inflammatory pathway [133]. Finally, the PPARγ agonist piaglitozone is known to display immunosuppressive properties and, in a small clinical cohort, significantly improves ASD symptoms, including irritability, lethargy, stereotypy and hyperactivity [134]. Additional studies are needed to determine whether the immunomodulatory properties of these drugs are necessary to confer ameliorative effects on ASD symptoms.

Conclusion

Increasing evidence points to an immune involvement in the

development and/or persistence of ASD symptoms. Maternal immune activation is a principal environmental risk factor for ASD that is sufficient to cause autism-related behavioral abnormalities and neuropathologies in rodent and primate models. Gene x environment studies demonstrate that immune activation in the background of various genetic susceptibility factors, can exacerbate pre-existing abnormalities or perpetuate new ASD-associated endophenotypes. ASD-related autoantibodies represent another immune-mediated pathway affecting neurodevelopment and behavior, but additional studies in animal models are needed to identify the mechanisms underlying autoantibody production and action. ASD individuals also exhibit various aspects of immune dysregulation in the brain, periphery and GI tract. Still unknown are the etiologies and functional consequences of these immune abnormalities on ASD symptoms. Animal models will be useful for determining whether these endophenotypes impact core ASD behaviors and neuropathologies, and whether they converge with identified genetic and environmental risk factors for autism. Studies in these areas will sharpen our understanding of immunomodulatory approaches towards treating particular autism-associated endophenotypes in defined subclasses of ASD individuals.

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