Review

Altered Gut Microbiome in Autism Spectrum Disorder: Potential Mechanism and Implications for Clinical Intervention

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ABSTRACT

Autism spectrum disorder is a heterogeneous neurodevelopmental disorder with an increased prevalence around the world over the past two decades. Remarkably, a large number of individuals with ASD have gastrointestinal disorders. Recent studies demonstrate that the endogenous gut microbiota has a close relationship with ASD according to the analyses of human host intestinal microbial composition and animal model studies. Here, we review the reports of microbial dysbiosis in ASD, and then discuss the recent evidence of biological interactions among microbiota, metabolism, immunity, neurodevelopment, and behaviors. We also describe the role of the gut microbiome in the link between ASD and environmental risk factors. Finally, we suggest adjuvant treatments to consider in attempts to correct autistic behaviors.

KEYWORDS

Gut microbiome; autism spectrum disorder; clinical interventions

INTRODUCTION

Autism spectrum disorder (ASD) is a common neurodevelopmental disorder characterized by persistent deficits in social communication as well as unusually restricted and repetitive patterns of behavior or interests. Partly due to the changes in the diagnostic criteria, the prevalence of ASD has been reported from 0.60 to 2.64% [1–3]. The number of ASD cases was estimated at 62.6 million around the world in 2015, and the costs of the care for ASD children impose an enormous burden on families [4, 5]. In addition, individuals with ASD often experience co-morbid disorders including irritability, aggression, sleeping problems, developmental delay and epilepsy [6–8], which may cause additional medical expenses.

While population-based family studies estimate the heritability approximate 50–90% [9, 10], only a few comm-on variants that contribute to the heritability have been associated with ASD. Previous large-scale genetic studies have identified a number of rare variants such as copy number of variants and single point mutations [11], and the shared environmental influence was 30% [10]. ASD children often have gastrointestinal problems such as abdominal pain, diarrhea, and constipation [12–14], which are associated with the microbiome, in particular, evidence of *Sutterella* species have been found in the patients diagnosed with ASD but not in the control children with GI symptoms [15].

In this paper, we provide an overview of recent evidence about the interrelation among the gut microbiome, metabolism, immunology, and neurobiology. We review the epidemiological studies of gastrointestinal diseases and the composition of the gut microbiome in individuals with ASD, and then discuss gut-immune function, neurodevelopment, metabolism, and other environmental factors. Finally, we review the existing evidence at a molecular level that might suggest some possible therapeutic interventions.

GASTROINTESTINAL DISTURBANCES AND GUT MICROBIOTA

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While the prevalence of digestive problems in ASD individuals has been reported varying at 23–70%, there is evidence that individuals with ASD have more likelihood of having gastrointestinal disorders [12]. A study found a strong correlation between gastrointestinal symptoms with autism severity [16], and altered gut microbiota has been found in children with ASD.

Microorganisms in the gut are essential for the host and play a crucial role in digestion [17, 18]. Nondigestible nutrients such as polysaccharides and cellulose can be fermented by microbiota in the intestine to produce energy and short chain fatty acids [18]. The short chain fatty acids, including butyrate produced by a single bacteria strains, *Clostridium tyrobutyricum* (CBut), acetate and propionate produced by *Bacteroides thetaiotaomicron* (BEta), can influence the expression of the tight-junction proteins (ZO-1, occludin, claudin-5) which are related to blood-brain barrier permeability and thus may have a secondary impact on the function of the brain [19].

Meanwhile, individuals with ASD have a different composition of microbiota in the gut compared with the neurotypical-developed children (NTD) [20]. *Sutterella* were found in more than 50% of individuals with both ASD and intestinal dysfunction, but not in the NTD children with pure dysfunction of the gut [21,22]; and Kang reported lower levels of *Prevotella, Coprococcus*, and unclassified *Veillonellaceae* in the gut bacterial populations in children with ASD [23]. It has been indicated that changes in a few microbial species may lead to behavioral problems but the mechanism is not defined.

METABOLIC DISTURBANCE AND GUT MICROBIOME

The metabolic disturbance has been observed in individuals with ASD. Compared to their unaffected siblings and age-matched healthy controls, children with ASD children tend to have a distinct profile of metabolic phenotyping in urine [24]. Through a metabolomic analysis, docosahexaenoic acid (DHA) and sphingosine 1-phosph-ate (S1P) in serum have been found to be lower in individuals with autism [25] and an elevated level of p-cresol in urine has been identified and replicated in an independent study [26]. In the human gastrointestinal tract, symbiotic bacteria play an indispensable role in degrading nondigestible carbohydrates.

Animal studies suggest that those metabolic changes are likely due to an imbalance of the gut microbiome. Germ-free mice show a significant difference in metabolites in luminal contents of the colon compared with ex-germ free mice which were with a gavage of feces from specific pathogen-free mice [27], indicating that the microbiota may profoundly influence the colonic luminal metabolome. The metabolomic analysis also suggested that gut microflora have significant effects on mammalian blood metabolites [28].

When rats were treated with maternal high-fat diet (MHFD) for several weeks, the level of acetate dramatically increased due to the gut microbiota-food interaction. Acetate may increase glucose-stimulated insulin secretion (GSIS) across the activated parasympathetic nervous system [29]. This positive feedback may lead to the development of obesity as a critical element of the metabolic syndrome. Another study in mice shows that a high-fat diet altered the composition of gut microbiota including *Bifidobacterium*, which plays a functional role in barrier-protection [30]. Further, in contrast with mice with a gavage of heatkilled bacteria, mice with a gavage of *Akkermansia muciniphila* showed maintenance of the intestinal barrier and a reversal of high-fat-diet-induced metabolic disorders, including fat-mass gain and insulin resistance [31, 32].

Studies have shown that the gut microbiota modulates ASD-related behaviors and affect the levels of specific metabolites. Gastrointestinal barrier defect and alteration of microbiota have been noted in maternal immune activation (MIA) mouse model associated with ASD [33]. MIA offspring treated with the human commensal *Bacteroides fragilis* had a significant improvement in gut permeability, microbial composition, and ASD-related behaviors. This treatment also modulates the levels of several specific metabolites, suggesting that gut bacterial effect on the host metabolome affect behaviors. These findings support a gut-microbiome-brain connection in a mouse model of ASD.

IMMUNE DYSREGULATION AND GUT MICROBIOME

Immune dysregulation including maternal inflammation or infection may increase the vulnerability of neurodevelopment, such as ASD [34–38]. A study of brain tissues and cerebrospinal fluid (CSF) have shown an activation of microglia and astroglia or a marked increase in a small cytokine monocyte chemoattractant protein 1 (MCP1) in individuals with ASD [39]. A meta-analysis of 19 cytokines in plasma and serum from 17 studies shows that individuals with ASD have a marked elevation of prion-flammatory cytokines, including interleukin (IL)-1, IL-6, IL-8, interferon (IFN)-γ, eotaxin, MCP1 in blood com-pared with healthy controls [40]. However, consistent data are still lacking for other cytokines, likely due to the difference in the methodology, etiological variability and population heterogeneity [41–43].

The immune system and gut-resident microbes have a pronounced interaction [44]. In an animal model, MIA causes an ASD-like phenotype and the maternal inflammation during critical periods of the embryonic development leads to an alteration of the immune system and further disturbs the fetal environment, which may cause aberrant behaviors in offspring [45]. MIA male mice offspring show a lower rate of ultrasonic vocalizations, fewer harmonic, and more complex voice, which may continue into adulthood. Additionally, MIA offspring display increased repetitive or stereotyped behaviors, a mouse version of the core symptoms of autism [33, 45, 46]. The target region of MIA was located in the primary somato-sensory cortex (S1DZ) [47] where there was an increase in neural activities that project to the temporal association cortex (TeA) or striatum in this cortical region, which can in turn result in impaired sociability. More-over, the inhibition of neural activity is sufficient to sup-press the abnormal behaviors [47].

Despite the fact that immune activation contributes to abnormal behaviors, it is not clear how microbes participate in the induction of immune activation. In the germ-free mice, the introduction of gram-positive gut-residing segmented filamentous bacteria (SFB) can cause an autoimmune disorder [48]. SFB increase the number of T helper 17 (T_H17) cells, which differentiate from $CD4^+$T cells induced by the collaboration of TGF-b and IL-6 and secrete IL-17 in promoting inflammatory responses. Maternal colonization of SFB together with injection of poly (I:C) can stimulate the activity of T_H17 cells and lead to abnormal behaviors in offspring [49]. However, mice injected with poly (I:C) alone show a significant increase in TNFα and IFN-β compared with endotoxin-free phosphate-buffered saline (PBS)-injected mice, but not exhibit the change in the behaviors of offspring. Treatment of pregnant mice with vancomycin reducing SFB and the abnormal behaviors of offspring can be rescued [49]. In contrast to SFB, some other microbes are involved in suppressing the immune response in the host. Mucosal colonization of *Bacteroides fragilis* could supress T_H17 response in germ-free mice [50]. The underlying mechan-ism may be that the polysaccharide A on *Bactericides fragilis* promotes immunologic tolerance through incre-asing the proportion of regulatory T cells by action at the Toll-like receptor 2 [50,51].

Another potential bacterial modulator of MIA is the lipopolysaccharide (LPS) endotoxin located on the surface of gram-negative bacteria. LPS can bind the Toll-like receptor receptors, which that trigger an immune response. Maternal inflammation in mice triggered by LPS (*E. coli* serotype 0111:B4) can cause a proliferation of neural stem and progenitor cells in offspring, which also exhibited autism-associated behaviors including reduced ultrasonic vocalizations [52–54]. A study showed that offspring of rats with maternal immune activation by LPS had an alteration of specific gene expression profiles of interneuron migration and oxidative stress without a triggering a fetal immune response and exhibited reduced social and exploratory behaviors [55].

GUT MICROBIOME AND NEURODEVELOPMENT

The microbial composition and function in the intestine affect the development of nerve cells from the embryo to adulthood. These effects include the differentiation of neural stem cells, migration, and projection of immature neurons to their destinations, the growth of axons and dendrites, and the formation of synapses. While germ-free mice exhibited an increase in adult neurogenesis in the dorsal hippocampus, which plays a role in spatial learning and memory, the recolonization of microbiota in germ-free adult mice cannot change this tendency, suggesting a critical part of microbiota in early development life. This is consistent with the past demonstration that stress or long-term antibiotic treatment may potentially inhibit neurogenesis in the hippocampus [56].

Microglia are tissue macrophage cells located in the bra-in that participate in immune responses including rem-oval of dead cells and pathogens. Several studies found that marked activation and augmented number of micro-glia in different regions of the brain are pathophysiologic characteristics of ASD [39, 57, 58]. The complexities of host microbiota can contribute to maturation and function of microglia. Germ-free mice exhibited global defects in microglia with altered cell proportions and an immature phenotype, which show impaired innate immune responses to LPS. The full repertoire of microbes or SCFA is necessary and sufficient to restore impairment of microglia stability [59].

Administration of antibiotics to the pregnant mice not only influence gut microbiome composition but also affect the behavior of the offspring in locomotor activity and anxiety. It has been shown that the behaviors of the offspring from antibiotic-treatment pregnant-mice can be rescued at week 4 when normal pregnant mice fostered them from the post-natal day one [60]. Another study found that female rats exposed to a diet containing 1% succinyl sulfa thiazole, a non-absorbable antibiotic, during periconceptional period, can alter the offspring behaviors without maternal infection, also likely due to the alteration of maternal gut microbiota [61].

GUT MICROBIOME LINKS BETWEEN ASD AND ENVIRONMENTAL RISK FACTORS

Neurons are highly sensitive and vulnerable to environmental factors such as maternal stress in early development in humans, especially in the first three years. The method of delivery, breastfeeding, maternal separation and infection all may have an impact. The mode of obstetrical delivery has a significant influence on the com-position of the intestinal microbiota at the very beginning of human life [62, 63]. Epidemiological studies rep-ort that cesarean section (C-section) delivery is associated with the non-communicable chronic diseases including immune and metabolic disorders [64]. Children born by C-section including elective and emergency C-section are more likely to have ASD, although this tendency does not appears in sibling controls [65, 66]. Children delivered through C-section show a different pattern of gut microbiome compared to infants born via vaginal delivery. This differ-ence seen in C-section infants can be restored to that seen in vaginally delivered infants by exposure to maternal vaginal fluids [67].

Maternal stress is another environmental factor that may affect major physiological systems including neurodevelopmental disorders. Maternal stress increases the pro-inflammatory state of the fetal central nervous system, and such neuroimmune inflammation has been implic-ated in ASD [68]. The microbiome of the maternal vagina can be disturbed by the early-life stress and in turn influence the gut microbiome of offspring. For example, the decrease of *Lactobacillus* in the maternal vagina of the mouse model may lead to a reduction in the transmission of this bacterium to offspring, which influence the off-spring microbiota composition and metabolic processes that are essential for normal neurodevelopment [69]. In addition, prenatal stress induces impairment of novel object recognition memory in a rat model, which shows a significantly lower

memory index measured by novel object recognition test (NORT) [70].

Maternal infection with different types of agents (bacterial, viral, parasitic, and fungal) and site of infection (genitourinary infections and skin infections) during pregnancy is another risk factor that can increase the prevalence of abnormal behaviors associated with autism [71, 72]. Maternal infection affects the maternal immune responses and the fetal neurodevelopmental environment at a critical time. In utero exposure to valproic acid (VPA), a drug used to treat epilepsy and bipolar disorder, causes a change in the composition of gut microbiota and further influences metabolism in a murine model of ASD [73].

Maternal exposure to pesticides and certain fungicides such as pyraclostrobin, trifloxystrobin, famoxadone and fenamidone in the environment or the food, is associated with the neurodevelopmental disorders including ASD [74, 75]. All these chemicals produce transcriptional changes *in vitro* that are similar to those observed in brain samples from individuals with autism including stimulation of free radical production and disruption of micro-tubules in neurons. These effects can be reduced by pretreating with a microtubule stabilizer, an antioxidant, or with sulforaphane [76].

THE DIRECTION OF POTENTIAL INTERVENTIONS

So far, several potential mechanisms including immune, metabolic and neurological pathways have been implicated by the use of animal and cellular models, and each of these pathways can be considered as potential therapeutic targets for one or more phenotypes of ASD. First, psychotropic drugs including risperidone and aripiprazole are often used to improve behavioral symptoms of ASD. The atypical antipsychotic risperidone was the first drug approved by the FDA for treating repetitive behavior and hyperactivity, and it acts via modulation of the 5-HT and dopamine neuronal systems, which are related to ASD [77–81]. Second, sulforaphane or broccoli extracts can reduce free radical production and protect microtubules in neurons by inducing expression of Nrf2, which is a transcription factor that regulates the expression of antioxidant proteins and protect cells against oxidative damage [74, 82, 83]. ASD children taking oral sulforaphane for 18 weeks had improvement of phenotypes including social interaction and communication after discontinuing treatment about four weeks [76]. Third, oxytocin treatment or activating oxytocin neurons can also restore the ASD-like social behaviors in Cntnap2 knockout mice, which shows a reduced number of oxytocin neurons [84]. Detailed discussions of the mechanism relating oxytocin and neuromodulation in ASD as well as potential medical treatments have been presented in the literature in the past [85, 86].

Further, evidence shows the relationship between the intestinal microbiome and the function of the nervous system. It has become plausible to consider using commensal probiotics to treat neurodevelopment diseases such as ASD. For example, MIA mice offspring treated with a single organism, *Bacteroides fragilis*, show improved ASD-related defects in the core symptoms of communicative, stereotypic, anxiety-like and sensorimotor behaviors [33, 45]. In another study in mice, *Lactobacillus reuteri*as, a single probiotic and a commensal strain, corrected the social deficits in the MHFD offspring by inducing increased oxytocin [87].

Finally, fecal microbiota transplantation (FMT) has already been used to alleviate intestinal diseases such as irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD), presumably by correcting the composition of the gut microbiota [88–90]. A recent report indicates that Microbiota Transfer Therapy (MTT) and then an extended fecal microbiota transplant (FMT) can improve autism symptoms and alter the gut ecosystem [91]. In this open-label study, autistic individuals with moderate to severe gastrointestinal problems were treated with antibiotics for two weeks and then used a dose of standardized human gut microbiota for 7–8 weeks. ASD-related symptoms showed a significant improvement.

Although the prospects are promising, potential negative aspects of treatment on the subject must be considered. Children treated with risperidone do not improve core behaviors associated with autism, and improved symptoms will return to the original state when the drug is discontinued. Moreover, children showed a significant gain in weight due to an increased daily intake of food, especially carbohydrates that may have implications for risk of insulin resistance and metabolic syndrome [92]. Microbiota transplantation may also disturb the balance of the intestinal microbial composition. Individuals with recurrent *Clostridium difficile* infection who received FMT had adverse events such as diarrhea, abdominal discomfort, and even one death occurred because of aspiration during sedation for FMT administered via colonoscopy in the treatment of *Clostridium difficile* infection [93–96]. Whether diverse microbiota does benefit or harm to the homeostasis of the intestine are still unknown at present, and it is also not yet understood what microbes play vital roles in the healthy functioning of the gut. Therefore, in-depth characterization of defined communities or even various individual microbial species that may ameliorate ASD symptoms should be a focus in the future.

CONCLUSION

In summary, environmental risk factors contribute to the development of ASD and the role of the gut microbiome in host homeostasis is now well established. The gut microbiome influences metabolism, immunity, and neurophysiology and these converge to influence development processes in the brain and following behaviors (Figure 1). We have reviewed recent evidence for neuro-development and behavior changes in both animal models and humans as influenced by gut microbiome status for ASD-associated behaviors. However, the possible mechanism depends upon exposure to specific microbes, beneficial or pathogenic, induction of certain phenotypes in the immune system, the metabolic system, the central nervous system, or the enteric nervous system.

CONFLICTS OF INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this paper.

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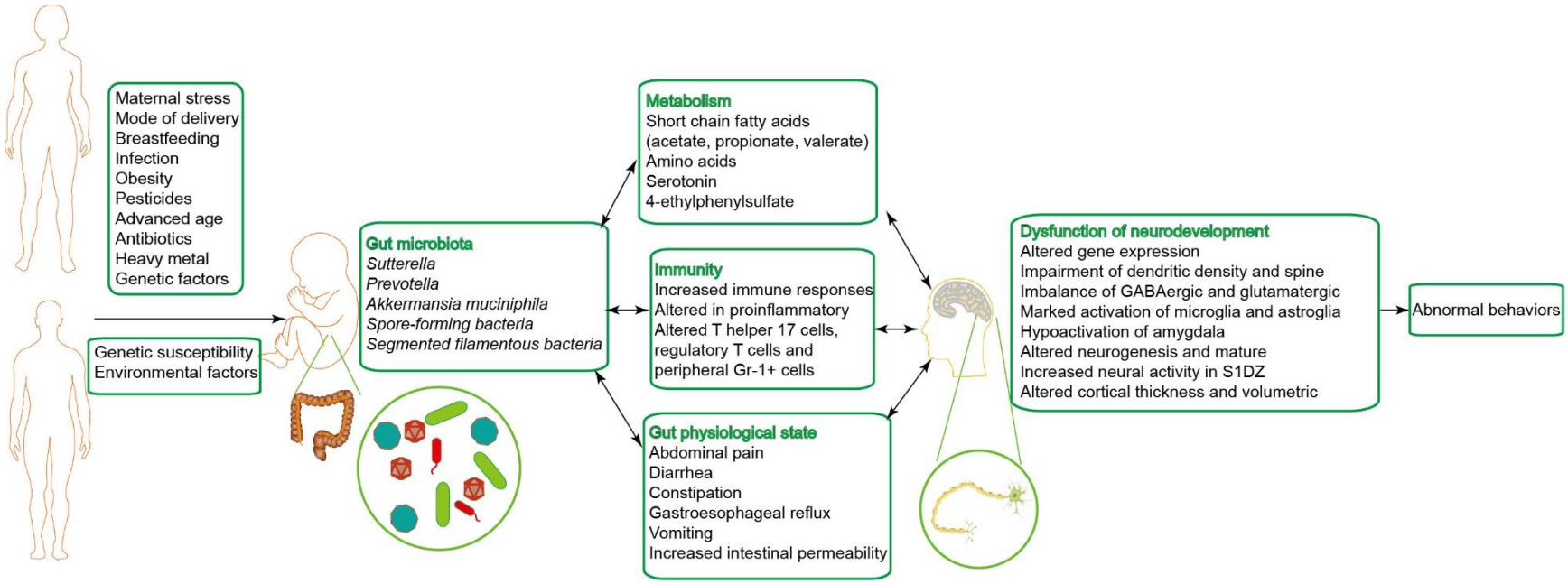

Figure 1. Schematic diagram illustrating the hypothesized role of the gut microbiome in autism spectrum disorder (ASD). Environmental exposures and genetic factors directly or indirectly affect microbiotic exposures. The microbiota interacts with gut immune physiology, metabolism and the brain, and these alterations elicit the abnormal behaviors of ASD.

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