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Commentary

Association Among Gut Microbes, Intestinal Physiology, and Autism

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Autism spectrum disorder (ASD) is a set of neurodevelopmental disorders characterized by two core symptoms: social deficits and increase in stereotypic/repetitive behaviors. Along with the core symptoms of ASD, other comorbid conditions can be observed in certain populations of people with ASD, such as gastrointestinal (GI) complications and altered gut microbiome (Adams et al., 2011; Parracho et al., 2005). Homeostasis of the GI system is closely regulated by the gut microbiota. Therefore, whether the gut microbiota is a contributing factor for ASD has been postulated recently. Several key questions have been raised. Do gut microbes contribute to the behavioral symptoms in ASD? How do gut microbes affect behavioral output through the gut–brain axis? How do gut and brain communicate with each other? Due to the complexity of the distal connection between gut and brain, these are the key questions that remain unanswered in the field.

In this issue of *EBioMedicine*, Golubeva et al. (2017) meticulously examine the gut microbiota and its association with host intestinal physiology and behavioral abnormalities in a murine model of ASD-BTBR mice. BTBR is an inbred mouse strain that exhibits several behavioral deficits related to ASD (McFarlane et al., 2008) compared with another strain, C57BL/6, which has been adopted as a control strain in mouse studies of ASD. Because the behavior deficits in BTBR mice are robust and closely relevant to ASD, investigating BTBR mice could provide an opportunity to identify therapeutic targets against ASD (Silverman et al., 2012). Altering the gut microbiota and providing the gut commensal bacteria have been demonstrated to have beneficial effects on ASD behaviors in both mouse models and humans (Hsiao et al., 2013; Kang et al., 2017). Golubeva et al. (2017) found that BTBR mice have a very distinct gut microbiota profile with low diversity. Moreover, the abundance of two major bacterial phyla in the gut is shifted toward an increase in Bacteroidetes and a decrease in Firmicutes. Several bacterial genera have been identified to be responsible for most of these changes in abundance. In addition, the main microbial metabolites are dysregulated in the digestive system of BTBR mice. The microbial profile indicates that the gut bacterial community in BTBR mice is impacted, which could result in dysregulation of GI homeostasis.

Intriguingly, GI motility and permeability are drastically altered in BTBR mice. Golubeva et al. (2017) found that BTBR mice have longer colons and lower GI motility. The low GI motility could be due to the dysregulation of serotonin metabolism in the gut and abnormal development of the enteric nervous system. Serotonin production in BTBR mice is lowered, with a compensatory increase in serotonin transporter in both the colon and the ileum. The structure and the number of neurons in the enteric nervous system are abnormally developed in BTBR mice. GI permeability has also been examined in BTBR mice. The function of the intestinal barrier is important for protection of the host from bacterial invasion (Groschwitz and Hogan, 2009). Interestingly, BTBR mice exhibit differential changes in GI permeability and its related genes in the ileum and the colon. Furthermore, electrolyte transport activity is reduced in both the ileum and the colon of BTBR mice. Impairment of the gut barrier could be associated with dysregulation of bile acid synthesis and metabolism in the gut, where BTBR mice generally have low levels of bile acid in the plasma but high levels of bile acid in the feces. The disruption of serotonin and bile acid levels in the gut in BTBR mice is plausibly related to the differences in gut microbiota, since gut bacteria involve in the regulation of host serotonin and bile acid levels (Sayin et al., 2013; Yano et al., 2015).

Golubeva et al. (2017) also tested BTBR with multiple ASD-related behavioral tasks, showing that BTBR mice exhibit impaired social behaviors, increased repetitive behaviors, increased anxiety-like behaviors, and cognitive dysfunction. The social neuropeptide oxytocin is down-regulated and the stress hormone corticosterone is up-regulated in BTBR mice. Interestingly, defecation is dramatically induced when BTBR mice are under stress. Altogether, these results indicate that

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intestinal homeostasis is disrupted in BTBR mice. However, whether these changes cause the behavioral abnormalities in BTBR mice is still unknown.

This study provides a very comprehensive data set that details the intestinal physiological features and behavior phenotypes in BTBR mice. The authors perform association analysis to further link specific gut bacteria with functional changes in BTBR mice. Several bacterial genera are significantly correlated with social behaviors, repetitive behaviors, and anxiety-like behaviors in BTBR mice. Among them, *Blautia* is correlated not only with social behaviors, but also with serotonin level and GI motility. Other bacterial genera, such as *Rikenella*, *Parabacteroides*, *Odoribacter*, *Desulfovibrio*, *Bifidobacterium*, *Bilophila*, and *Bacteroides*, are also correlated with behaviors and intestinal physiology (Golubeva et al., 2017). Correlation analysis among the functional alterations in BTBR mice could advance the development of precision microbiota-based therapeutics for ASD.

The BTBR strain is one of the most recognized and reproducible animal models for ASD and has been well characterized by several independent laboratories. This study undoubtedly provides key information toward understating the mechanisms by which gut microbial dysbiosis contributes to ASD-like behaviors. To further extend the significant findings and prove the concept proposed in this study, examination of the effects of manipulation of serotonin and bile acid levels in the gut on GI motility, GI permeability, and behavioral changes in BTBR mice would be crucial to establish the cause–effect relationship. Furthermore, to examine the specific bacterial targets identified here, establishing a gnotobiotic BTBR mouse model or supplementing BTBR mice with gut commensal bacteria would be another direction that could complement this study. Finally, pinpointing the convergent microbial phenotypes among various mouse models of ASD will help us to understand the common features of microbial dysbiosis in ASD. In conclusion, this study opens several promising directions to guide researchers in the field to elucidate the role of gut bacteria in ASD.

Disclosure

The author declares no conflicts of interest.

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