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The Gut Microbiota - The Environmental Causative Factor and the Potential Therapeutic Targets of Autism Spectrum Disorder

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Autism spectrum disorder (ASD) is a neurodevelopment mental disorder affecting approximately 1-2% of the population. ASD patients displayed a wide range of symptoms including social interaction difficulties, decreased communication skills, restricted activities and repetitive behavior [1]. The etiology of ASD involves both genetic and environmental factors according to previous research [2]. Up to now, more than 200 susceptible genes have been identified in ASD patients with different patterns of inheritance [3]. Meanwhile, the gut microbiota emerged as important environmental factors and played a pivotal role in the development and treatment of ASD.

The paediatricians first observed that ASD children frequently accompany with gastrointestinal symptoms [4]. Previous clinical and biological researches have demonstrated that the disturbance in the gut microbiota caused by antibiotic application served as a potential risk factor to the development of ASD [5-7]. The human gut harbors at least more than 1,000 different species of known bacteria [8]. The first colonization of the gut microbiota comes from a natural complex microbiota exposure when the infant is delivered vaginally [9]. The diet and other environmental factors including infection and subsequent antibiotics application definitely alter the natural composition of the gut microbiota [10]. Altered composition of the gut microbiota have been confirmed to be the causative factor for sorts of diseases including ASD. High-throughput sequencing identifies two predominant bacterial species in the human microbiota: the Bacteroidetes and Firmicutes phyla, with the Proteobacteria, Actinobacteria, Fusobacteria, and Verrucomicrobia phyla occurring relatively rare [11]. Clostridia, Bacteriodetes and Desulfovibrio were proved to promote autistic behaviors in ASD [12-15]. In addition, the level of Bacteroidetes was found to be higher in the stools of severe ASD children, while as the level of Firmicutes higher in the control group. Also, short-chain fatty acids (SCFAs) played an important role during the processing [14,15].

The microbiota-gut-brain axis, a well-known neurohumoral communication system performs bidirectionally and its disturbance was found in ASD subjects [16]. According to previous research, the bidirectional microbiota-gut-brain axis mainly acts through neuroendocrine, neuroimmune and autonomic nervous mechanisms. Signals from the gut microbiota influence brain function through microbiota metabolites such as SCFAs [14,15]. Meanwhile, the brain sends messages to the gut to impact microbiota activity and gastrointestinal physiology through serotonin (5-hydroxytryptamine or 5-HT) and other neurotransmitters. 5-HT is a monoamine that plays an important regulatory role in many organ systems [17,18]. Previous research has demonstrated a direct metabolic signalling of gut microbiota to 5-HT release [19]. The gut microbiota can also act through SCFAs to promote the enteric 5-HT production and homeostasis [20]. In addition, recent publication reported specific finding in ASD that altered blood–brain barrier integrity could be couple with increased neuroinflammation which possibly impaired gut barrier integrity [21]. More research will be performed to elucidate the specific mechanisms of how gut microbiota imbalances lead to ASD and to provide potential therapeutic targets to ASD.

The potential therapeutic benefit of re-establishing the balance of the gut microbiota was first demonstrated through mouse model of ASD [22-24]. The investigators applied a maternal immune activation (MIA) mouse model as ASD model and gave MIA offspring oral treatment of human commensal Bacteroides fragilis. The research demonstrated that the probiotic treatment could correct the gut permeability, alter the gut microbial composition, and ameliorate defects of the ASD mouse model in communicative ability, anxiety-like and sensorimotor behaviors, etc. [22]. The results supported the gut-microbiome-brain connection in the mouse model of ASD and identified a potential therapeutic target. Another recent report also indicated that maternal high-fat diet could induce a shift in gut microbial ecology and negatively impact offspring's ASD-like social behavior [25]. Clinical case study also observed reduced severity of abdominal symptoms and improvement of ASD core symptoms after a multi-strain mixture of ten probiotics treatment for 4 weeks and followed by a four month follow-up observation on a 12 year old boy with ASD and severe cognitive disabilities [26]. Taken together, application of probiotics and certain special diet supplement may be a promising strategy to treat ASD. More translational biomedical research including ASD models studies and long-term follow-up clinical research need to be developed and further researches are needed to elucidate the biological mechanisms and set up optimal treatment protocol for ASD [27].

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