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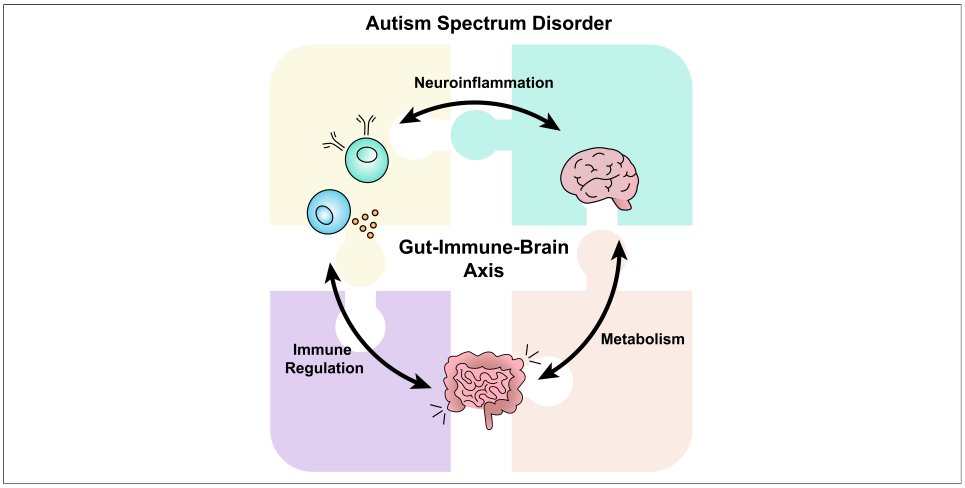
New insights into the gut-immune-brain axis: immune mechanisms and therapeutic targets for autism spectrum disorder

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INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that is estimated to affect 1 in 31 children in the United States as of 2025[1]. With rising prevalence and lack of effective prevention or treatment strategies, the disorder has captured the attention of the public in recent years. Despite large-scale research, the etiology of ASD remains debated. Genetics is a significant factor in ASD, with up to a thousand different genes involved and a heritability estimate of 80%[2]. However, large genetic variability across studies and cohorts suggests that non-genetic factors also contribute to its etiology. Among them, ASD patients are often found to harbor unique gut microbial signatures and immune phenotypes, coalescing to form the theory of a 'gut-immune-brain axis' in ASD[3].

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Evidence for a Gut-Microbial Link in ASD

Some of the earliest evidence supporting the gut-brain theory for ASD came from clinical observations of gastrointestinal (GI) disorders, including constipation, diarrhea, and abdominal pain, among patients[4]. ASD patients are two- to four-fold more likely to develop GI disorders compared to healthy individuals[5]. Notably, the presence of GI disorders is often correlated with higher severity of ASD behavioral symptoms, including repetitive behavior, social withdrawal, irritability, and anxiety[6,7]. The gut microbiota is a major regulator of GI disorders, contributing to both the pathogenesis and serving as a potential avenue for treatment[8]. It is estimated that 3.8×10^{13} bacterial cells from over 3,000 species reside in the human gut[9]. These gut microbes closely interact with the host to facilitate digestion, produce essential metabolites, and even regulate the host immune system. Motivated by comorbidity and the recent boom of the 'microbiome era', significant efforts have been made to study the ASD gut microbiome. The gut microbiota of ASD patients is often characterized by dysbiosis, with altered diversity and richness compared with neurotypical individuals[10]. While specific gut microbial compositions differ from study to study, ASD patients generally have elevated abundances of *Clostridium, Streptococcus, Lactobacillus,* and *Bacteroides* and lower levels of *Bifidobacterium, Akkermansia, Prevotella,* and *Bacteroidetes*[11-14]. Notably, gut microbial dysbiosis in ASD often shares similarities with signatures observed in inflammatory guts and GI disorders, including elevated *Firmicutes/Bacteroidetes* ratios, lower diversities, and higher abundances of *Lactobacillus, Bacteroides*, and *Escherichia/Shigella*[15-17]. However, these phyla and genera comprise vast arrays of bacterial species, and each strain can exert different physiological and immunological effects. Therefore, genera correlations may not accurately reflect the functional properties of each bacterial species, prompting more in-depth studies into the role of distinct gut microbes in ASD.

Microbiome correlations among ASD patients have even spurred causation studies using animal models of ASD. Germ-free (GF) C57BL/6 (B6) mice are characterized by altered behaviors, including stress responses, anxiety, sociability, learning, and motor functions[18,19]. In a milestone study, the transfer of fecal microbiota from either neurotypical individuals or ASD patients induced corresponding behavioral phenotypes in GF B6 mice, suggesting that microbiota alone, even in the absence of genetic factors, could result in ASD phenotypes[20]. In another study using valproic acid-induced rats, microbiota transplantation regulated short-chain fatty acid (SCFA) and neurotransmitter levels, altering behavior[21].

The gut-brain axis is evident even in genetic models of ASD. For instance, although BTBR mice are genetically predisposed to ASD phenotypes, symptoms are absent in GF-derived BTBR mice[22]. Additionally, gut microbiota transplantation from B6 mice confers neurotypical behaviors in BTBR mice, suggesting that the gut microbiome regulates behavior even in the context of ASD genetics[22]. In the *Cntnp2* knockout mouse model, social behavior is regulated specifically by the gut microbiota, while host genetics regulates hyperactivity[23]. This highlights the unique interplay between 'nurture' and 'nature' in mouse models of ASD. In both models, microbiome manipulations alter the metabolite pool, suggesting a pathway through which the gut-brain axis may regulate ASD.

Analyses of blood metabolites have revealed elevated levels of lactate, glutamate, histidine, and free fatty acids, among others, in ASD pateints[11,24,25]. Additionally, a recent longitudinal study of patients found that the majority of the metabolic differences in ASD are accounted for by 14 key biochemical pathways, which are marked by decreases in glutathione, carnosine, 5'-methyltetrahydrofolic acid, and CoQ10, and increases in lactate, glycerol, alanine, threonine, cholesterol, and ceramides[26]. Importantly, the gut microbiota is responsible for the production of key neurotransmitters and their precursors, including dopamine, levodopa, tyrosine, serotonin, tryptophan, glutamate, glutamine, and gamma-aminobutyric acid (GABA)[11]. Altered levels of some of these neurotransmitters have been observed in ASD patients, including higher levels of glutamate, glutamine, serotonin, and lower levels of GABA[27-29]. Although the flow of major gut-derived

neurotransmitters is tightly regulated by the blood-brain barrier, their effects can be mediated through both precursors and signaling through the vagus nerve[30]. With accumulating metagenomic and correlative data among patients, many studies have hypothesized direct connections between gut microbial metabolites and their functional roles on the brain.

CRITICISMS OF THE GUT-BRAIN THEORY IN ASD

However, despite growing support for the gut-brain theory, critics have also raised concerns. Concerns have regarded the methodology of human ASD microbiome studies, ranging from sample size, cohort age, ethnicities, and geography, to sample storage and sequencing techniques[31]. These differences may often result in inconsistencies in findings across studies[31]. For instance, despite large-scale efforts to characterize the ASD microbiome, cross-regional comparisons have often failed to identify significant shared markers. For example, a study comparing ASD cohorts across Shenzhen and Moscow revealed that although 119 to 130 ASD-specific species were identified in each cohort, respectively, only two species, *Eubacterium_sp_CAG_248* and *Prevotella copri,* were found in both[32].

These concerns have prompted debate as to whether the gut microbiota is a consequence, rather than cause, of ASD. For example, dietary intake preferences among ASD patients can, in and of itself, alter these outcomes[33]. Compared to neurotypical children, ASD patients were observed to have reduced variety and overall quality of food, with higher intake of simple carbohydrates, lower fruit and vegetable variety, and lower protein intake[34]. ASD cohorts have also exhibited greater preference for high-fat/salt and energy-dense foods, with more cheese, processed meats, and oily fish consumption[35]. Overall, observable gut microbiome differences in ASD patients can be directly correlated with restricted dietary interests and less-diverse diets[33]. However, while these criticisms raise valid concerns about rushing to causal conclusions, they fail to define the directionality in the relationship between the gut microbiota and dietary preferences. More importantly, they also overlook the immunological implications of the gut microbiota and the role of the immune system in ASD.

THE IMMUNE SYSTEM AS A MEDIATOR OF THE GUT MICROBIOTA AND ASD

The gut microbiota is a fundamental educator of the host immune system. Numerous studies using GF mice have shown major defects in both adaptive and innate immune compartments[36,37]. The microbiota can be fine-tuned to poise the immune system towards either a more inflammatory or anti-inflammatory phenotype[38-40]. For instance, microbiota-derived SCFA's, including butyrate and propionate, are potent drivers of regulatory T cells (Tregs), while acetate can induce type 1 interferons[41,42]. This evidence suggests that changes in the ASD metabolome may elicit functional differences in the host immune system. For example, a longitudinal study of 205 ASD patients identified disruptions in metabolic pathways related to reduced anti-inflammatory and antioxidant defenses[26]. Network pharmacology analyses also revealed that, among 51 key genes regulated by microbial metabolites, IL-17, IL-6, and PI3K/Akt pathways were the most affected[43]. Notably, the analyses highlight the ability to trace specific metabolites and their producers to distinct physiological pathways, providing greater resolution into understanding how the gut microbiota directly regulates host immune responses during ASD[43].

In line with this background, immune dysfunction itself has been recognized as a major comorbidity of ASD. ASD patients are more likely to develop allergies and autoimmune disorders, such as type 1 diabetes and atopic dermatitis[44]. Additionally, plasma cytokine levels of ASD patients are marked by higher levels of proinflammatory interferon (IFN)-γ, interleukin (IL)-1β, IL-6, IL-17, IL-12, and tumor necrosis factor (TNF)-α, while postmortem brain samples have elevated TNF-α, IL-6, IFN-γ, IL-8, and granulocyte-macrophage colony-stimulating factor (GM-CSF) levels[45-47]. These observations raise the question of whether inflammation is a causal factor in ASD.

Inflammation during pregnancy is a known risk factor for ASD and is demonstrated by the maternal immune activation (MIA) mouse model. The MIA model utilizes segmented filamentous bacteria (SFB)-mediated IL-17A production to directly elicit ASD-associated behaviors[48]. Inflammation-driven ASD is also demonstrated in BTBR mice, which are characterized by heightened peripheral inflammatory markers, as well as greater numbers of inflammatory CD4 and CD8 T cells within the brain[22,47,49]. In BTBR mice, suppressing CD4 T cells is sufficient to reduce neuroinflammation and reduce abnormal neuronal activity, resulting in neurotypical behavior[22]. Interestingly, these gut-immune dynamics may be partly attributable to links between the intestinal and blood-brain barrier permeability[50,51]. For example, gut barrier permeability in BTBR mice directly controls inflammatory cytokine markers within the brain, as well as mouse behavior[52]. These emerging studies demonstrate the role of the host immune system in driving ASD in a mouse model. However, further mechanistic studies are required to solidify this gut-immune-brain axis, and translational relevance necessitates analyses of brain-resident T cells from human ASD patient samples to identify their origins and licensing mechanisms.

NEW PARADIGMS IN NEUROIMMUNE INTERACTIONS

Emerging findings suggest that the effect of inflammatory cytokines on brain function may be more nuanced than previously held[11]. For instance, IFN-γ is required for normal social behaviors, and even IL-17A, which causes ASD when elevated prenatally, can improve social behaviors in adult MIA mice[53,54]. This dichotomy may be explained by the downstream signals these cytokines elicit. Various neurons express cytokine receptors, including those for TNF-α, IL-1β, IL-6, IL-4, IL-13, and IFN-γ, and each cytokine can prompt distinct neuronal activities[55]. For example, basolateral amygdala neurons co-express both IL-17R and IL-10R[56]. Administration of IL-17A and IL-17C can induce anxiogenic behaviors by increasing the excitability of these neurons, whereas IL-10 has the opposite effect, demonstrating that specific cytokines can exert distinct outcomes even within the same neurons[56]. Cytokine signaling with neurons also affects other ASD-related behaviors, such as social withdrawal. It was recently demonstrated that serotonergic neurons within the dorsal raphe nucleus express IL-1R1[57]. IL-1β, including that from the periphery, and lipopolysaccharide induce social withdrawal in mice by acting on these neurons, highlighting another immune axis that regulates social behavior[57].

Furthermore, the recent discovery of brain-resident T cells sheds light on this unique immune-brain link. In recent years, several studies using mouse models have demonstrated causal roles within the gut-immune-brain axis [Figure 1]. In milestone back-to-back publications, brain-resident CD4 T cells were demonstrated to be conduits between the gut and the brain in mice. Large populations of IFN-γ-producing CD4 T cells were identified in the brain parenchyma, localizing within the subfornical organ, brain stem, thalamus, and cerebellum[58,59]. Interestingly, these T cells feature nuanced roles that are dependent on the gut microbiota. For example, during homeostasis, IFN-γ-producing T cells are required for normal food-seeking behavior[58]. However, IFN-γ and IL-17A can also elicit neuroinflammation and microglial activation when brain-resident T cells are licensed by SFB[59]. Taken together, these preclinical studies suggest that brain-resident T cells may be a key to unlocking the gut-immune-brain axis.

TARGETING THE GUT-IMMUNE-BRAIN AXIS FOR THERAPEUTICS

Theories of a gut-brain etiology in ASD have spurred numerous clinical and preclinical studies that test the efficacy of microbiota-based therapeutics, including probiotics. Across mouse models of ASD, probiotic strains, such as *L. reuteri, Bacteroides fragilis, B. dentium,* and *E. faecalis*, have shown efficacy in improving ASD-related behaviors[23,60-64]. However, clinical evidence remains sparse, and certain species used in mouse models, such as *E. faecalis,* may be opportunistic pathogens that require scrutiny when being considered for use in human patients. A few studies have shown mild improvements in ASD patients using consortium

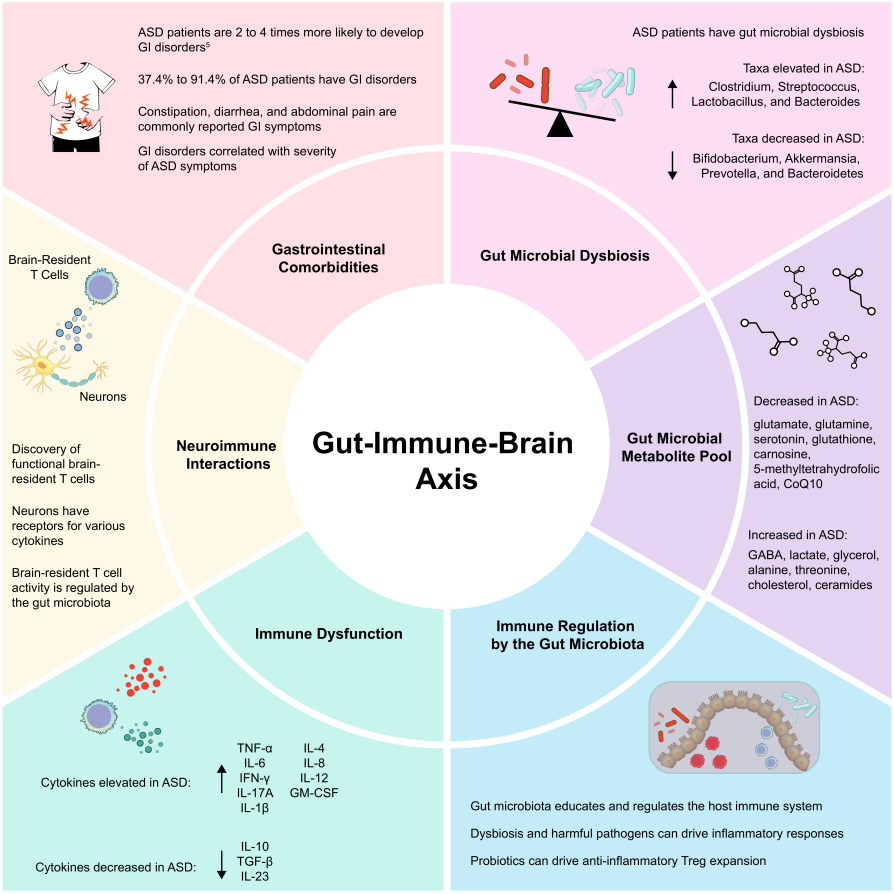


Figure 1. Evidence supporting a gut-immune-brain axis in ASD. ASD patients show comorbidities with gastrointestinal disorders and immune dysregulation, marked by elevated inflammatory cytokines. These clinical observations have prompted extensive investigation into the gut microbial composition in ASD and the associated metabolic signatures. As major regulators of host immunity, the gut microbiota and their metabolites influence peripheral immune responses within the central nervous system, providing a potential mechanistic link between gut dysbiosis and ASD pathophysiology. Created using Adobe Illustrator. ASD: Autism spectrum disorder; TNF-α: tumor necrosis factor-α; IL: interleukin; TGF-β: Transforming growth factor-β; GM-CSF: granulocyte-macrophage colony-stimulating factor; GABA: gamma-aminobutyric acid; IFN-γ: interferon-γ.

probiotics, but these were limited to GI and psychiatric symptoms and partial behavioral phenotypes, and not overall autism severity[65-67].

Major limitations preventing widespread clinical success of probiotics may stem from patient heterogeneity. Diets, immune backgrounds, genetics, and lifestyles influence gut microbial composition and may impact the ability of probiotics to colonize and function within each patient. This suggests that microbiota-based therapeutics require further optimization, including personalized therapies, to improve clinical efficacy. Furthermore, to develop more effective consortium probiotics, the overall metabolic and immunological impact of the consortium should be assessed, as opposed to those of individual species. This will require in-depth analyses of the functional characteristics and interactions among the strains, particularly in the context of each patient's existing microbiome.

With these considerations, addressing the gut-immune link in ASD may enable more effective therapeutic strategies that target multiple axes simultaneously. For instance, SCFA-producing *Clostridium butyricum* has shown potential to alleviate behavioral abnormalities in BTBR and valproic acid mouse models by enhancing gut barrier function and reducing proinflammatory cytokines[68]. Additionally, *L. reuteri*-based probiotic

treatment, which can improve the metabolic profile and reduce inflammation, can induce anti-inflammatory Tregs, reduce neuroinflammation, and improve ASD-associated behaviors in BTBR mice[22]. In rat models of ASD, administration of *B. longum* and synbiotics, such as the combination of *L. rhamnosus* and luteolin, improves the metabolite pool and lowers proinflammatory cytokine levels within the brain[69,70]. These preclinical studies highlight the ability of microbiota-based therapeutics to regulate ASD-associated metabolite pools, reduce inflammation, and thereby ameliorate behavioral outcomes.

CONCLUSIONS

Uncertainties about the etiology of ASD make it difficult to establish causal directions across pathways, limiting the development of effective therapeutics. However, accumulating data from clinical and animal studies point to the gut microbiota and host immunity as essential components of ASD pathogenesis. Importantly, emerging evidence from animal models indicates that the gut microbiota and its metabolites may act independently of ASD genetics. Immune responses to the gut microbiota and its metabolites may bridge the gut and the brain by regulating neuroinflammation. Future microbiota-based therapeutics should aim to target each component of this axis to achieve greater therapeutic efficacy.

DECLARATIONS

Authors' contributions

Designed and wrote the manuscript: Park JC
Supervised manuscript preparation and provided conceptual supervision: Im SH

Availability of data and materials

Not applicable.

AI and AI-assisted Tools Statement

Not applicable.

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Conflicts of interest

Im SH is the founder and major shareholder of ImmunoBiome. Im SH is an Executive Editor of the journal *Microbiome Research Reports*. Im SH was not involved at any stage of the editorial process, including reviewers' selection, manuscript handling, and decision-making. Park JC declares there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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REFERENCES

1. Shaw KA, Williams S, Patrick ME, et al. Prevalence and early identification of autism spectrum disorder among children aged 4 and 8 years - autism and developmental disabilities monitoring network, 16 sites, United States, 2022. *MMWR Surveill Summ.* 2025;74:1-22. DOI PubMed PMC

2. Gogate A, Kaur K, Khalil R, et al. The genetic landscape of autism spectrum disorder in an ancestrally diverse cohort. *NPJ Genom Med.* 2024;9:62. DOI PubMed PMC
3. Park JC, Im SH. The gut-immune-brain axis in neurodevelopment and neurological disorders. *Microbiome Res Rep.* 2022;1:23. DOI PubMed PMC
4. Hung LY, Margolis KG. Autism spectrum disorders and the gastrointestinal tract: insights into mechanisms and clinical relevance. *Nat Rev Gastroenterol Hepatol.* 2024;21:142-63. DOI PubMed
5. Neuhaus E, Bernier RA, Tham SW, Webb SJ. Gastrointestinal and psychiatric symptoms among children and adolescents with autism spectrum disorder. *Front Psychiatry.* 2018;9:515. DOI PubMed PMC
6. Chakraborty P, Carpenter KLH, Major S, et al. Gastrointestinal problems are associated with increased repetitive behaviors but not social communication difficulties in young children with autism spectrum disorders. *Autism.* 2021;25:405-15. DOI
7. Nikolov RN, Bearss KE, Lettinga J, et al. Gastrointestinal symptoms in a sample of children with pervasive developmental disorders. *J Autism Dev Disord.* 2009;39:405-13. DOI
8. Hou K, Wu ZX, Chen XY, et al. Microbiota in health and diseases. *Signal Transduct Target Ther.* 2022;7:135. DOI PubMed PMC
9. Sender R, Fuchs S, Milo R. Revised Estimates for the number of human and bacteria cells in the body. *PLoS Biol.* 2016;14:e1002533. DOI PubMed PMC
10. Osama A, Anwar AM, Ezzeldin S, et al. Integrative multi-omics analysis of autism spectrum disorder reveals unique microbial macromolecules interactions. *J Adv Res.* 2025;77:265-79. DOI PubMed PMC
11. Park JC, Chang L, Kwon HK, Im SH. Beyond the gut: decoding the gut-immune-brain axis in health and disease. *Cell Mol Immunol.* 2025;22:1287-312. DOI PubMed PMC
12. Iglesias-Vázquez L, Van Ginkel Riba G, Arija V, Canals J. Composition of gut microbiota in children with autism spectrum disorder: a systematic review and meta-analysis. *Nutrients.* 2020;12:792. DOI PubMed PMC
13. Li N, Yang J, Zhang J, et al. Correlation of gut microbiome between ASD children and mothers and potential biomarkers for risk assessment. *Genom Proteom Bioinf.* 2019;17:26-38. DOI PubMed PMC
14. Wang L, Christophersen CT, Sorich MJ, Gerber JP, Angley MT, Conlon MA. Low relative abundances of the mucolytic bacterium *Akkermansia muciniphila* and *Bifidobacterium* spp. in feces of children with autism. *Appl Environ Microbiol.* 2011;77:6718-21. DOI PubMed PMC
15. Strati F, Cavalieri D, Albanese D, et al. New evidences on the altered gut microbiota in autism spectrum disorders. *Microbiome.* 2017;5:24. DOI PubMed PMC
16. Tomova A, Husarova V, Lakatosova S, et al. Gastrointestinal microbiota in children with autism in Slovakia. *Physiol Behav.* 2015;138:179-87. DOI
17. Kim HS, Oh SJ, Kim BK, et al. Dysbiotic signatures and diagnostic potential of gut microbial markers for inflammatory bowel disease in Korean population. *Sci Rep.* 2024;14:23701. DOI PubMed PMC
18. Diaz Heijtz R, Wang S, Anuar F, et al. Normal gut microbiota modulates brain development and behavior. *Proc Natl Acad Sci U S A.* 2011;108:3047-52. DOI PubMed PMC
19. Chu C, Murdock MH, Jing D, et al. The microbiota regulate neuronal function and fear extinction learning. *Nature.* 2019;574:543-8. DOI PubMed PMC
20. Sharon G, Cruz NJ, Kang DW, et al. Human gut microbiota from autism spectrum disorder promote behavioral symptoms in mice. *Cell.* 2019;177:1600-1618.e17. DOI PubMed PMC
21. Zhong J, Zhu B, Zou Z, et al. Gut microbiota mediates the beneficial effects of exercise on autism-like behaviors. *BMC Microbiol.* 2026;26:157. DOI PubMed PMC
22. Park JC, Sim MA, Lee C, et al. Gut microbiota and brain-resident $CD4^+$ T cells shape behavioral outcomes in autism spectrum disorder. *Nat Commun.* 2025;16:6422. DOI PubMed PMC
23. Buffington SA, Dooling SW, Sgritta M, et al. Dissecting the contribution of host genetics and the microbiome in complex behaviors. *Cell.* 2021;184:1740-1756.e16. DOI PubMed PMC
24. Barone R, Alaimo S, Messina M, et al.; MIMIC-Autism Group. A subset of patients with autism spectrum disorders show a distinctive metabolic profile by dried blood spot analyses. *Front Psychiatry.* 2018;9:636. DOI PubMed PMC
25. Orozco JS, Hertz-Picciotto I, Abbeduto L, Slupsky CM. Metabolomics analysis of children with autism, idiopathic-developmental delays, and down syndrome. *Transl Psychiatry.* 2019;9:243. DOI PubMed PMC
26. Lingampelly SS, Naviaux JC, Heuer LS, et al. Metabolic network analysis of pre-ASD newborns and 5-year-old children with autism spectrum disorder. *Commun Biol.* 2024;7:536. DOI PubMed PMC
27. Abdulamir HA, Abdul-Rasheed OF, Abdulghani EA. Serotonin and serotonin transporter levels in autistic children. *Saudi Med J.* 2018;39:487-94. DOI PubMed PMC

28. Kubota M, Yoshihara Y, Uwatoko T, et al. Elevated brain glutamine levels in adults with autism spectrum disorder: a 7T MRS study. *Mol Psychiatry.* 2026;31:3062-9. DOI PubMed PMC
29. Hassan TH, Abdelrahman HM, Abdel Fattah NR, et al. Blood and brain glutamate levels in children with autistic disorder. *Res Autism Spect Dis.* 2013;7:541-8. DOI
30. Jameson KG, Kazmi SA, Ohara TE, et al. Select microbial metabolites in the small intestinal lumen regulate vagal activity via receptor-mediated signaling. *iScience.* 2025;28:111699. DOI PubMed PMC
31. Mitchell KJ, Dahly DL, Bishop DVM. Conceptual and methodological flaws undermine claims of a link between the gut microbiome and autism. *Neuron.* 2026;114:196-211. DOI PubMed
32. Wang W, Fu P. Gut microbiota analysis and *in silico* biomarker detection of children with autism spectrum disorder across cohorts. *Microorganisms.* 2023;11:291. DOI PubMed PMC
33. Yap CX, Henders AK, Alvares GA, et al. Autism-related dietary preferences mediate autism-gut microbiome associations. *Cell.* 2021;184:5916-5931.e17. DOI
34. Mathew NE, Mallitt KA, Masi A, et al. Dietary intake in children on the autism spectrum is altered and linked to differences in autistic traits and sensory processing styles. *Autism Res.* 2022;15:1824-39. DOI PubMed PMC
35. Wu Y, Wong OWH, Chen S, et al. Gut microbiome mediates the causal link between autism spectrum disorder and dietary preferences: a mendelian randomization study. *Int J Mol Sci.* 2026;27:2006. DOI PubMed PMC
36. Zheng D, Liwinski T, Elinav E. Interaction between microbiota and immunity in health and disease. *Cell Res.* 2020;30:492-506. DOI PubMed PMC
37. Park JC, Im SH. Of men in mice: the development and application of a humanized gnotobiotic mouse model for microbiome therapeutics. *Exp Mol Med.* 2020;52:1383-96. DOI PubMed PMC
38. Verma R, Lee C, Jeun EJ, et al. Cell surface polysaccharides of *Bifidobacterium bifidum* induce the generation of Foxp3$^+$ regulatory T cells. *Sci Immunol.* 2018;3:eaat6975. DOI PubMed
39. Lee C, Kim SW, Verma R, et al. Probiotic consortium confers synergistic anti-inflammatory effects in inflammatory disorders. *Nutrients.* 2024;16:790. DOI PubMed PMC
40. Sharma G, Sharma A, Kim I, et al. A dietary commensal microbe enhances antitumor immunity by activating tumor macrophages to sequester iron. *Nat Immunol.* 2024;25:790-801. DOI
41. Smith PM, Howitt MR, Panikov N, et al. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. *Science.* 2013;341:569-73. DOI PubMed PMC
42. Antunes KH, Fachi JL, de Paula R, et al. Microbiota-derived acetate protects against respiratory syncytial virus infection through a GPR43-type 1 interferon response. *Nat Commun.* 2019;10:3273. DOI PubMed PMC
43. Zhang F, Xu W, Tang Q, Huang J. The identification of metabolites from gut microbiota in autism spectrum disorder via network pharmacology. *Sci Rep.* 2025;15:31765. DOI PubMed PMC
44. Chen M, Su T, Chen Y, et al. Comorbidity of allergic and autoimmune diseases in patients with autism spectrum disorder: a nationwide population-based study. *Res Autism Spect Dis.* 2013;7:205-12. DOI
45. Enstrom AM, Van de Water JA, Ashwood P. Autoimmunity in autism. *Curr Opin Investig Drugs.* 2009;10:463-73. PubMed PMC
46. Zhao H, Zhang H, Liu S, Luo W, Jiang Y, Gao J. Association of peripheral blood levels of cytokines with autism spectrum disorder: a meta-analysis. *Front Psychiatry.* 2021;12:670200. DOI PubMed PMC
47. Li X, Chauhan A, Sheikh AM, et al. Elevated immune response in the brain of autistic patients. *J Neuroimmunol.* 2009;207:111-6. DOI PubMed PMC
48. Kim S, Kim H, Yim YS, et al. Maternal gut bacteria promote neurodevelopmental abnormalities in mouse offspring. *Nature.* 2017;549:528-32. DOI PubMed PMC
49. Heo Y, Zhang Y, Gao D, Miller VM, Lawrence DA. Aberrant immune responses in a mouse with behavioral disorders. *PLoS One.* 2011;6:e20912. DOI PubMed PMC
50. Di L, Huang P, He Y, Sun N, Chi L, Huang L. Gut dysbiosis is associated with increased blood-brain barrier permeability and cognitive impairment in elderlies with coronary heart disease. *Front Aging Neurosci.* 2025;17:1640761. DOI PubMed PMC
51. Braniste V, Al-Asmakh M, Kowal C, et al. The gut microbiota influences blood-brain barrier permeability in mice. *Sci Transl Med.* 2014;6:263ra158. DOI PubMed PMC
52. Li F, Ke H, Wang S, et al. Leaky gut plays a critical role in the pathophysiology of autism in mice by activating the lipopolysaccharide-mediated toll-like receptor 4-myeloid differentiation factor 88-nuclear factor kappa B signaling pathway. *Neurosci Bull.* 2023;39:911-28. DOI PubMed PMC
53. Filiano AJ, Xu Y, Tustison NJ, et al. Unexpected role of interferon-γ in regulating neuronal connectivity and social behaviour. *Nature.* 2016;535:425-9. DOI PubMed PMC

54. Reed MD, Yim YS, Wimmer RD, et al. IL-17a promotes sociability in mouse models of neurodevelopmental disorders. *Nature.* 2020;577:249-53. DOI PubMed PMC
55. Zipp F, Bittner S, Schafer DP. Cytokines as emerging regulators of central nervous system synapses. *Immunity.* 2023;56:914-25. DOI PubMed PMC
56. Lee B, Kwon JT, Jeong Y, et al. Inflammatory and anti-inflammatory cytokines bidirectionally modulate amygdala circuits regulating anxiety. *Cell.* 2025;188:2190-2202.e15. DOI PubMed PMC
57. Yang L, Andina ML, Witkowski M, et al. IL-1R1-positive dorsal raphe neurons drive self-imposed social withdrawal in sickness. *Cell.* 2026;189:272-286.e19. DOI PubMed PMC
58. Yoshida TM, Nguyen M, Zhang L, et al. The subfornical organ is a nucleus for gut-derived T cells that regulate behaviour. *Nature.* 2025;643:499-508. DOI PubMed PMC
59. White Z, Cabrera I, Mei L, et al. Gut inflammation promotes microbiota-specific CD4 T cell-mediated neuroinflammation. *Nature.* 2025;643:509-18. DOI
60. Sgritta M, Dooling SW, Buffington SA, et al. Mechanisms underlying microbial-mediated changes in social behavior in mouse models of autism spectrum disorder. *Neuron.* 2019;101:246-259.e6. DOI PubMed PMC
61. Nettleton JE, Klancic T, Schick A, et al. Prebiotic, probiotic, and synbiotic consumption alter behavioral variables and intestinal permeability and microbiota in BTBR mice. *Microorganisms.* 2021;9:1833. DOI PubMed PMC
62. Hsiao EY, McBride SW, Hsien S, et al. Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. *Cell.* 2013;155:1451-63. DOI PubMed PMC
63. Wu WL, Adame MD, Liou CW, et al. Microbiota regulate social behaviour via stress response neurons in the brain. *Nature.* 2021;595:409-14. DOI PubMed PMC
64. Engevik MA, Luck B, Visuthranukul C, et al. Human-derived bifidobacterium dentium modulates the mammalian serotonergic system and gut-brain axis. *Cell Mol Gastroenterol Hepatol.* 2021;11:221-48. DOI PubMed PMC
65. Santocchi E, Guiducci L, Prosperi M, et al. Effects of probiotic supplementation on gastrointestinal, sensory and core symptoms in autism spectrum disorders: a randomized controlled trial. *Front Psychiatry.* 2020;11:550593. DOI PubMed PMC
66. Mazzone L, Dooling SW, Volpe E, et al. Precision microbial intervention improves social behavior but not autism severity: a pilot double-blind randomized placebo-controlled trial. *Cell Host Microbe.* 2024;32:106-116.e6. DOI
67. Hassib L, Kanashiro A, Pedrazzi JFC, et al. Microbiota-based therapies as novel targets for autism spectrum disorder: a systematic review and meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry.* 2025;139:111385. DOI
68. Liu S, Xi H, Xue X, et al. *Clostridium butyricum* regulates intestinal barrier function via trek1 to improve behavioral abnormalities in mice with autism spectrum disorder. *Cell Biosci.* 2024;14:95. DOI PubMed PMC
69. Alsubaiei SRM, Alfawaz HA, Almubarak AY, Alabdali NA, Ben Bacha A, El-Ansary A. Independent and combined effects of probiotics and prebiotics as supplements or food-rich diets on a propionic-acid-induced rodent model of autism spectrum disorder. *Metabolites.* 2022;13:50. DOI PubMed PMC
70. Abuaish S, Al-Otaibi NM, Aabed K, et al. The efficacy of fecal transplantation and bifidobacterium supplementation in ameliorating propionic acid-induced behavioral and biochemical autistic features in juvenile male rats. *J Mol Neurosci.* 2022;72:372-81. DOI

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