The Gut–Liver–Brain Axis

Subjects: Toxicology

Contributor: Danielle Qiuyun Jiang

The gut–liver–brain axis constitutes a multidirectional communication network that connects the enteric, hepatic, and central nervous systems. Through the complex interplay between the gut–liver, gut–brain, and liver–brain axes, this communication network extends to involve endocrine, immune (humoral), and metabolic routes of communication. Within the network, the gut and liver affect cognitive behaviors through the host's immune responses and the regulation of microbiota, and the brain also influences intestinal and hepatic activities. Studies in animals have shown that an impaired gut–liver–brain axis is associated with diseases such as hepatic encephalopathy, Alzheimer's disease, Parkinson's disease, Multiple Sclerosis, depression, and autism spectrum disorder (ASD).

autism PFAS acetaminophen gut–liver–brain axis

1. Gut–Brain Interactions

The gut microbiota modulates gastrointestinal homeostasis in experimental animals through direct and indirect chemical signaling with the nervous system [1][2]. An example of direct signaling is the regulated expression of brain-derived neurotrophic factor (BDNF), a neuronal factor associated with depression, by short-chain fatty acids (SCFAs) produced in the gut [3]. SCFAs are lipids produced by the gut microbiome that can influence the central nervous system (CNS) through the regulation of the immune system, neuroplasticity, expression of various genes, and epigenetic changes [3]. The gut microbiome can also influence the host's appetite, feeding behaviors, and digestion through indirect chemical signaling. For example, within gut epithelium, the microbiota can regulate the production of endocrine signals, such as the hormone glucagon-like peptide 1 (GLP-1), from the enteroendocrine cells [4]. As such, germ-free (GF) mice that lack an endogenous microbiota have lower food consumption as compared to conventional mice with intact microbiota [5]. In addition, the gut microbiota has been related to the typical ASD behaviors in mice. For example, GF mice exhibit anti-sociality and prefer to spend time exploring an empty compartment as compared to where another mouse companion is present [6]. Diets play a part in brain health as well. Foods high in sodium trigger a proinflammatory response in the intestine, e.g., increased secretion by T helper 17 (TH17) cells of the proinflammatory cytokine interleukin-17 (IL-17) into the bloodstream. IL-17, in turn, inhibits the production of nitric oxide by neuroparenchymal vascular endothelial cells, impairing cerebral perfusion and thus cognition [7].

The gut microbiota also modulates the production and synthesis of neurotransmitters in the hosts. For example, in silico and in vitro studies [8][9] have shown that microorganisms such as Bacteriodes, Bifidobacterium, Parabacteriodes, and Escherichia spp. can produce γ-aminobutyric acid (GABA), a neurotransmitter that regulates

neuronal cell hyperactivity associated with stress, anxiety, and fear [10]. In vivo studies in rats using Bifidobacterium strains from humans [8] and cell culture studies [11] have shown an upregulated expression of GABA. However, it has not been demonstrated that the GABA produced by Bifidobacterium is resorbed from the gut and circulates in the body to affect the brain. In male GF mice, gut bacteria, through interacting with the enteroendocrine cells, play a vital role in the production of serotonin (5-hydroxytryptamine), a neurotransmitter that regulates body functions such as mood, cognition, learning, reward, memory, digestion, wound healing, and sexual desire [12]. The production of serotonin can be affected by microbial metabolites such as SCFAs, tryptophan, indole, and secondary bile acids [13][14]. It is also important to note that most neurotransmitters produced by the microbiota, such as serotonin, aminobutyric acid, and dopamine, cannot reach the brain directly due to the blood–brain barrier. However, in rats [15], neurotransmitters can cross the blood–brain barrier indirectly through neurotransmitter precursors, such as tryptophan (serotonin precursor), before being converted into active neurotransmitters [16][17] [18]. The mechanisms of neurotransmitters produced from the gut microbiota to influence the functions of other body parts have not been well-established, presenting an avenue for future research focusing on the interactions between the gut and brain. It was hypothesized that, in the gut, tryptophan undergoes three major metabolic pathways, e.g., the 5-HT, kynurenine, and AhR ligand pathways, which may be directly or indirectly controlled by saprophytic flora [19].

The major neuronal pathway facilitating gut–brain interactions is the vagus nerve that extends from the brainstem to innervate both the gut and enteric nervous system [20]. Influenced by the gut microbiota, the enteroendocrine cells produce chemical stimuli, such as neurotransmitters, hormones, and metabolites, to trigger the production of chemoreceptors that activate mechanoreceptors to relay signals from the vagus nerve to the CNS [21]. Neurotransmitters, integral to the gut–brain interactions, can be produced by the gut microbiota through the metabolism of indigestible fibers such as cellulose, lignin, beta-glucans, and pectin. Specifically, dopamine and norepinephrine are produced by members of the Bacillus family; GABA by the Bifidobacteria family; GABA and acetylcholine by the Lactobacilli family; norepinephrine and serotonin by the Escherichia family; and serotonin by the Enterococcus and Streptococcus families [22]. In addition, Bacteroides spp. regulate the development of enteric cells in mice, which play important roles in the maintenance of neuronal networks and regulation of gut homeostasis [23][24]. Healthy development and activation of microglia, the innate immune cells of the brain, are likewise modulated by microbiota. In separate studies, GF mice treated with SCFAs and Bifidobacterium spp. exhibited restoration of microglial morphology and functions [25][26].

2. Gut–Liver Interactions

Gut dysbiosis can contribute to metabolic disorders in the liver of both humans and experimental animals, such as alcoholic and non-alcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis, primary sclerosing cholangitis, cholestatic liver disease, hepatocellular carcinoma, and cirrhosis [27][28][29][30][31][32][33][34]. In the bidirectional relationship, communication with each other is connected through the portal vein, biliary tract, and systemic circulation in humans. From the intestine, microbial metabolites are transported to the liver through the

portal vein. Meanwhile, to maintain gut eubiosis and control bacterial overgrowth, bile salts and antimicrobial molecules are transported from the liver to the intestinal lumen through the biliary tract [35][36][37].

In mice, an impaired synergistic relationship within the gut microbiota can lead to gut dysbiosis and reduce the activation of important receptors such as membrane G protein-coupled receptor TGR5 and nuclear bile acid receptor FXR. Such impairment can lead to a decrease in secondary bile acids synthesis, followed by the retention of bile salt, bacterial overgrowth, and liver disease that may potentially progress to liver failure [38][39]. One example would be hepatic encephalopathy, a typical disease model of a dysregulated gut–liver–brain axis. Symptoms from hepatic encephalopathy can be alleviated by improving the axis via treatment with Lactobacillus in mice [40] and fecal translocation in mice with steatohepatitis [41][42]. It was recently postulated that in mice and humans, a sustained damage to the inner gut vascular barrier in the gastrointestinal tract is a key player along the gut–liver–brain axis, as it has the ability to influence beyond the liver to distal organs including the brain [43].

3. Liver–Brain Interactions

Hepatic dysfunction can lead to CNS dysfunction through alterations in CNS blood flow, the presence of inflammatory metabolites, excess bile acids, and accumulation of neurotoxic compounds such as ammonia in mice [44][45][46]. In patients with chronic liver conditions, neurological symptoms such as fatigue, anxiety, social withdrawal, depression, and sleep disturbance have been observed [47]. It has been recently shown that potential mechanistic avenues within the gut–liver–brain axis may be altered in the setting of chronic liver diseases, which subsequently contribute to the neurological disorders mentioned above [48][49][50][51][52][53].

Cytokine-mediated signaling is thought to affect the neurotransmission within the basal ganglia and cause CNS dysfunction. In the setting of intrahepatic inflammation, liver immune cells produce proinflammatory cytokines such as IL-6, IL-1β, and tumor necrosis factor (TNF)-α. These inflammatory cytokines can induce neurological changes by affecting the peripheral neural signaling; they can also enter the CNS through systemic circulation and the disrupted blood–brain barrier to affect the neurons within [54].

The vagus nerve, as mentioned in the section on gut–brain interactions, is the major neuronal pathway for the communication between the gastrointestinal tract and CNS. The vagus nerve is bilateral, with the left and right nerves in part having distinct functions. In several studies, the left vagus nerve has been shown to carry the signals from the liver to the brain [55]. Through this pathway, recent work has portrayed a new neuroimmune pathway in which the liver has demonstrated gut-dependent sensing and signaling to promote an anti-inflammatory state through the brain. Upon the sensing of luminal contents in the gastrointestinal tract, the liver afferent vagal fibers transmit sensory inputs to the nucleus tractus solitarius of the brainstem to induce and maintain gut T-regulatory cells through enteric neurons and parasympathetic nerve signaling [56].

References

1. Cryan, J.F.; O'Riordan, K.J.; Cowan, C.S.; Sandhu, K.V.; Bastiaanssen, T.F.; Boehme, M.; Codagnone, M.G.; Cussotto, S.; Fulling, C.; Golubeva, A.V.; et al. The microbiota-gut-brain axis. Physiol. Rev. 2019, 99, 1877–2013.
2. Martin, C.R.; Osadchiy, V.; Kalani, A.; Mayer, E.A. The brain-gut-microbiome axis. Cell. Mol. Gastroenterol. Hepatol. 2018, 6, 133–148.
3. Dalile, B.; Van Oudenhove, L.; Vervliet, B.; Verbeke, K. The role of short-chain fatty acids in microbiota–gut–brain communication. Nat. Rev. Gastroenterol. Hepatol. 2019, 16, 461–478.
4. Clemmensen, C.; Müller, T.D.; Woods, S.C.; Berthoud, H.-R.; Seeley, R.J.; Tschöp, M.H. Gut-Brain Cross-Talk in Metabolic Control. Cell 2017, 168, 758–774.
5. Bäckhed, F.; Ding, H.; Wang, T.; Hooper, L.V.; Koh, G.Y.; Nagy, A.; Semenkovich, C.F.; Gordon, J.I. The Gut Microbiota as an Environmental Factor That Regulates Fat Storage. Proc. Natl. Acad. Sci. USA 2004, 101, 15718–15723.
6. Desbonnet, L.; Clarke, G.; Shanahan, F.; Dinan, T.G.; Cryan, J.F. Microbiota is essential for social development in the mouse. Mol. Psychiatry 2014, 19, 146–148.
7. Faraco, G.; Brea, D.; Garcia-Bonilla, L.; Wang, G.; Racchumi, G.; Chang, H.; Buendia, I.; Santisteban, M.M.; Segarra, S.G.; Koizumi, K.; et al. Dietary salt promotes neurovascular and cognitive dysfunction through a gut-initiated TH17 response. Nat. Neurosci. 2018, 21, 240–249.
8. Duranti, S.; Ruiz, L.; Lugli, G.A.; Tames, H.; Milani, C.; Mancabelli, L.; Mancino, W.; Longhi, G.; Carnevali, L.; Sgoifo, A.; et al. Bifidobacterium adolescentis as a key member of the human gut microbiota in the production of GABA. Sci. Rep. 2020, 10, 14112.
9. Otaru, N.; Ye, K.; Mujezinovic, D.; Berchtold, L.; Constancias, F.; Cornejo, F.A.; Pugin, B. GABA production by human intestinal Bacteroides spp.: Prevalence, regulation, and role in acid stress tolerance. Front. Microbiol. 2021, 12, 656895.
10. Strandwitz, P.; Kim, K.H.; Terekhova, D.; Liu, J.K.; Sharma, A.; Levering, J.; McDonald, D.; Dietrich, D.; Ramadhar, T.R.; Lekbua, A.; et al. GABA-modulating bacteria of the human gut microbiota. Nat. Microbiol. 2019, 4, 396–403.
11. Pokusaeva, K.; Johnson, C.; Luk, B.; Uribe, G.; Fu, Y.; Oezguen, N.; Matsunami, R.K.; Lugo, M.; Major, A.; Mori-Akiyama, Y.; et al. GABA-producing Bifidobacterium dentium modulates visceral sensitivity in the intestine. Neurogastroenterol. Motil. 2016, 29, e12904.
12. Clarke, G.; Grenham, S.; Scully, P.; Fitzgerald, P.; Moloney, R.D.; Shanahan, F.; Dinan, T.G.; Cryan, J.F. The microbiome-gut-brain axis during early life regulates the hippocampal serotonergic system in a sex-dependent manner. Mol. Psychiatry 2013, 18, 666–673.
13. Morris, G.; Berk, M.; Carvalho, A.; Caso, J.R.; Sanz, Y.; Walder, K.; Maes, M. The Role of the Microbial Metabolites Including Tryptophan Catabolites and Short Chain Fatty Acids in the

Pathophysiology of Immune-Inflammatory and Neuroimmune Disease. Mol. Neurobiol. 2017, 54, 4432–4451.

14. Yano, J.M.; Yu, K.; Donaldson, G.P.; Shastri, G.G.; Ann, P.; Ma, L.; Nagler, C.R.; Ismagilov, R.F.; Mazmanian, S.K.; Hsiao, E.Y. Indigenous Bacteria from the Gut Microbiota Regulate Host Serotonin Biosynthesis. Cell 2015, 161, 264–276.
15. Fernstrom, J.D.; Coppola, A.; Wenner, B.R.; Ilkayeva, O.; Stevens, R.D.; Maggioni, M.; Slotkin, T.A.; Levin, E.D.; Newgard, C.B.; O'Kane, R.L.; et al. Role of precursor availability in control of monoamine biosynthesis in brain. Physiol. Rev. 1983, 63, 484–546.
16. Banks, W.A. Characteristics of compounds that cross the blood-brain barrier. BMC Neurol. 2009, 9, S3.
17. Ding, J.-H.; Jin, Z.; Yang, X.-X.; Lou, J.; Shan, W.-X.; Hu, Y.-X.; Du, Q.; Liao, Q.-S.; Xie, R.; Xu, J.-Y. Role of gut microbiota via the gut-liver-brain axis in digestive diseases. World J. Gastroenterol. 2020, 26, 6141–6162.
18. Johnson, K.V.-A.; Foster, K.R. Why does the microbiome affect behaviour? Nat. Rev. Genet. 2018, 16, 647–655.
19. Bosi, A.; Banfi, D.; Bistoletti, M.; Giaroni, C.; Baj, A. Tryptophan Metabolites Along the Microbiota-Gut-Brain Axis: An Interkingdom Communication System Influencing the Gut in Health and Disease. Int. J. Tryptophan Res. 2020, 13, 1178646920928984.
20. Morais, L.H.; Schreiber, H.L., IV; Mazmanian, S.K. The gut microbiota–brain axis in behaviour and brain disorders. Nat. Rev. Microbio. 2021, 19, 241–255.
21. Bellono, N.W.; Bayrer, J.R.; Leitch, D.B.; Castro, J.; Zhang, C.; O'Donnell, T.A.; Brierley, S.M.; Ingraham, H.A.; Julius, D. Enterochromaffin Cells Are Gut Chemosensors that Couple to Sensory Neural Pathways. Cell 2017, 170, 185–198.
22. Guo, T.L.; Chen, Y.; Xu, H.S.; McDonough, C.M.; Huang, G. Gut microbiome in neuroendocrine and neuroimmune interactions: The case of genistein. Toxicol. Appl. Pharmacol. 2020, 402, 115130.
23. Aktar, R.; Parkar, N.; Stentz, R.; Baumard, L.; Parker, A.; Goldson, A.; Brion, A.; Carding, S.; Blackshaw, A.; Peiris, M. Human resident gut microbe Bacteroides thetaiotaomicron regulates colonic neuronal innervation and neurogenic function. Gut Microbes 2020, 11, 1745–1757.
24. Kabouridis, P.S.; Lasrado, R.; McCallum, S.; Chng, S.H.; Snippert, H.J.; Clevers, H.; Pettersson, S.; Pachnis, V. Microbiota Controls the Homeostasis of Glial Cells in the Gut Lamina Propria. Neuron 2015, 85, 289–295.
25. Erny, D.; Hrabě de Angelis, A.L.; Jaitin, D.; Wieghofer, P.; Staszewski, O.; David, E.; Keren-Shaul, H.; Mahlakoiv, T.; Jakobshagen, K.; Buch, T.; et al. Host microbiota constantly control maturation

and function of microglia in the CNS. Nat. Neurosci. 2015, 18, 965–977.

26. Luck, B.; Engevik, M.A.; Ganesh, B.P.; Lackey, E.P.; Lin, T.; Balderas, M.; Major, A.; Runge, J.; Luna, R.A.; Sillitoe, R.V.; et al. Bifidobacteria shape host neural circuits during postnatal development by promoting synapse formation and microglial function. Sci. Rep. 2020, 10, e54176.
27. Bajaj, J.S.; Heuman, D.M.; Hylemon, P.B.; Sanyal, A.J.; White, M.B.; Monteith, P.; Noble, N.A.; Unser, A.B.; Daita, K.; Fisher, A.R.; et al. Altered profile of human gut microbiome is associated with cirrhosis and its complications. J. Hepatol. 2014, 60, 940–947.
28. Behary, J.; Amorim, N.; Jiang, X.-T.; Raposo, A.; Gong, L.; McGovern, E.; Ibrahim, R.; Chu, F.; Stephens, C.; Jebeili, H.; et al. Gut microbiota impact on the peripheral immune response in non-alcoholic fatty liver disease related hepatocellular carcinoma. Nat. Commun. 2021, 12, 187.
29. Kang, K.; Sun, Y.; Pan, D.; Sang, L.-X.; Sun, M.-J.; Li, Y.-L.; Chang, B. Distinctive gut microbial dysbiosis between chronic alcoholic fatty liver disease and metabolic-associated fatty liver disease in mice. Exp. Ther. Med. 2021, 21, 418.
30. Kim, H.-N.; Joo, E.-J.; Cheong, H.S.; Kim, Y.; Kim, H.-L.; Shin, H.; Chang, Y.; Ryu, S. Gut Microbiota and Risk of Persistent Nonalcoholic Fatty Liver Diseases. J. Clin. Med. 2019, 8, 1089.
31. Lang, S.; Demir, M.; Martin, A.; Jiang, L.; Zhang, X.; Duan, Y.; Gao, B.; Wisplinghoff, H.; Kasper, P.; Roderburg, C.; et al. Intestinal Virome Signature Associated With Severity of Nonalcoholic Fatty Liver Disease. Gastroenterology 2020, 159, 1839–1852.
32. Lapidot, Y.; Amir, A.; Nosenko, R.; Uzan-Yulzari, A.; Veitsman, E.; Cohen-Ezra, O.; Davidov, Y.; Weiss, P.; Bradichevski, T.; Segev, S.; et al. Alterations in the Gut Microbiome in the Progression of Cirrhosis to Hepatocellular Carcinoma. mSystems 2020, 5, 10–1128.
33. Liao, L.; Schneider, K.M.; Galvez, E.J.C.; Frissen, M.; Marschall, H.-U.; Su, H.; Hatting, M.; Wahlström, A.; Haybaeck, J.; Puchas, P.; et al. Intestinal dysbiosis augments liver disease progression via NLRP3 in a murine model of primary sclerosing cholangitis. Gut 2019, 68, 1477–1492.
34. Ponziani, F.R.; Bhoori, S.; Castelli, C.; Putignani, L.; Rivoltini, L.; Del Chierico, F.; Sanguinetti, M.; Morelli, D.; Sterbini, F.P.; Petito, V.; et al. Hepatocellular Carcinoma Is Associated With Gut Microbiota Profile and Inflammation in Nonalcoholic Fatty Liver Disease. Hepatology 2019, 69, 107–120.
35. Almeida, J.I.; Tenreiro, M.F.; Martinez-Santamaria, L.; Guerrero-Aspizua, S.; Gisbert, J.P.; Alves, P.M.; Serra, M.; Baptista, P.M. Hallmarks of the human intestinal microbiome on liver maturation and function. J. Hepatol. 2021, 76, 694–725.
36. Stärkel, P.; Schnabl, B. Bidirectional Communication between Liver and Gut during Alcoholic Liver Disease. Semin. Liver Dis. 2016, 36, 331–339.

37. Tripathy, D.; Grammas, P. Acetaminophen protects brain endothelial cells against oxidative stress. Microvasc. Res. 2009, 77, 289–296.

38. De Oliveira, M.C.; Gilglioni, E.H.; de Boer, B.A.; Runge, J.H.; de Waart, D.R.; Salgueiro, C.L.; Gaemers, I.C. Bile acid receptor agonists INT747 and INT777 decrease oestrogen deficiency-related postmenopausal obesity and hepatic steatosis in mice. Biochim. Et Biophys. Acta (BBA) Mol. Basis Dis. 2016, 1862, 2054–2062.

39. Sinal, C.J.; Tohkin, M.; Miyata, M.; Ward, J.M.; Lambert, G.; Gonzalez, F.J. Targeted Disruption of the Nuclear Receptor FXR/BAR Impairs Bile Acid and Lipid Homeostasis. Cell 2000, 102, 731–744.

40. Liu, Y.; Chen, K.; Li, F.; Gu, Z.; Liu, Q.; He, L.; Shao, T.; Song, Q.; Zhu, F.; Zhang, L.; et al. Probiotic Lactobacillus rhamnosus GG Prevents Liver Fibrosis Through Inhibiting Hepatic Bile Acid Synthesis and Enhancing Bile Acid Excretion in Mice. Hepatology 2019, 71, 2050–2066.

41. Zhong, W.; Wei, X.; Hao, L.; Lin, T.-D.; Yue, R.; Sun, X.; Guo, W.; Dong, H.; Li, T.; Ahmadi, A.R.; et al. Paneth Cell Dysfunction Mediates Alcohol-related Steatohepatitis Through Promoting Bacterial Translocation in Mice: Role of Zinc Deficiency. Hepatology 2019, 71, 1575–1591.

42. Zhou, D.; Pan, Q.; Shen, F.; Cao, H.-X.; Ding, W.-J.; Chen, Y.-W.; Fan, J.-G. Total fecal microbiota transplantation alleviates high-fat diet-induced steatohepatitis in mice via beneficial regulation of gut microbiota. Sci. Rep. 2017, 7, 1529.

43. Spadoni, I.; Zagato, E.; Bertocchi, A.; Paolinelli, R.; Hot, E.; Di Sabatino, A.; Caprioli, F.; Bottiglieri, L.; Oldani, A.; Viale, G.; et al. A gut-vascular barrier controls the systemic dissemination of bacteria. Science 2015, 350, 830–834.

44. Claeys, W.; Van Hoecke, L.; Geerts, A.; Van Vlierberghe, H.; Lefere, S.; Van Imschoot, G.; Van Wonterghem, E.; Ghesquière, B.; Vandenbroucke, R.E.; Van Steenkiste, C. A mouse model of hepatic encephalopathy: Bile duct ligation induces brain ammonia overload, glial cell activation and neuroinflammation. Sci. Rep. 2022, 12, 17558.

45. Deng, P.; Barney, J.; Petriello, M.C.; Morris, A.J.; Wahlang, B.; Hennig, B. Hepatic metabolomics reveals that liver injury increases PCB 126-induced oxidative stress and metabolic dysfunction. Chemosphere 2019, 217, 140–149.

46. Xie, G.; Wang, X.; Jiang, R.; Zhao, A.; Yan, J.; Zheng, X.; Huang, F.; Liu, X.; Panee, J.; Rajani, C.; et al. Dysregulated bile acid signaling contributes to the neurological impairment in murine models of acute and chronic liver failure. EBioMedicine 2018, 37, 294–306.

47. D'mello, C.; Swain, M.G. Liver–brain interactions in inflammatory liver diseases: Implications for fatigue and mood disorders. Brain Behav. Immun. 2014, 35, 9–20.

48. De Vadder, F.; Kovatcheva-Datchary, P.; Goncalves, D.; Vinera, J.; Zitoun, C.; Duchampt, A.; Bäckhed, F.; Mithieux, G. Microbiota-Generated Metabolites Promote Metabolic Benefits via Gut-

Brain Neural Circuits. Cell 2014, 156, 84–96.

49. Haghikia, A.; Jörg, S.; Duscha, A.; Berg, J.; Manzel, A.; Waschbisch, A.; Hammer, A.; Lee, D.-H.; May, C.; Wilck, N.; et al. Dietary Fatty Acids Directly Impact Central Nervous System Autoimmunity via the Small Intestine. Immunity 2015, 43, 817–829.
50. Hollingsworth, K.G.; Jones, D.E.J.; Taylor, R.; Frith, J.; Blamire, A.M.; Newton, J.L. Impaired cerebral autoregulation in primary biliary cirrhosis: Implications for the pathogenesis of cognitive decline. Liver Int. 2010, 30, 878–885.
51. McDonald, C.; Newton, J.; Lai, H.M.; Baker, S.N.; Jones, D.E. Central nervous system dysfunction in primary biliary cirrhosis and its relationship to symptoms. J. Hepatol. 2010, 53, 1095–1100.
52. Newton, J.L.; Hollingsworth, K.G.; Taylor, R.; El-Sharkawy, A.M.; Khan, Z.U.; Pearce, R.; Sutcliffe, K.; Okonkwo, O.; Davidson, A.; Burt, J.; et al. Cognitive impairment in primary biliary cirrhosis: Symptom impact and potential etiology. Hepatology 2008, 48, 541–549.
53. Sanmarco, L.M.; Wheeler, M.A.; Gutiérrez-Vázquez, C.; Polonio, C.M.; Linnerbauer, M.; Pinho-Ribeiro, F.A.; Li, Z.; Giovannoni, F.; Batterman, K.V.; Scalisi, G.; et al. Gut-licensed IFNγ+ NK cells drive LAMP1+TRAIL+ anti-inflammatory astrocytes. Nature 2021, 590, 473–479.
54. Nguyen, H.H.; Swain, M.G. Avenues within the gut-liver-brain axis linking chronic liver disease and symptoms. Front. Neurosci. 2023, 17, 1171253.
55. Matsubara, Y.; Kiyohara, H.; Teratani, T.; Mikami, Y.; Kanai, T. Organ and brain crosstalk: The liver-brain axis in gastrointestinal, liver, and pancreatic diseases. Neuropharmacology 2022, 205, 108915.
56. Teratani, T.; Mikami, Y.; Nakamoto, N.; Suzuki, T.; Harada, Y.; Okabayashi, K.; Hagihara, Y.; Taniki, N.; Kohno, K.; Shibata, S.; et al. The liver–brain–gut neural arc maintains the Treg cell niche in the gut. Nature 2020, 585, 591–596.