Review

Discovery Medicine 2025; 37(195): 608–617
https://doi.org/10.24976/Discov.Med.202537195.53

GPCRs With mTOR Signaling Expressed in Gut-Brain-Immune Axis-Cells Could Contribute to the Treatment of Neurodegenerative Diseases and Immune-Related Diseases

Akari Fukumoto[1], Naoko Suga[1], Moeka Nakashima[1], Satoru Matsuda[1,*]

[1]Department of Food Science and Nutrition, Nara Women's University, 630-8506 Nara, Japan
*Correspondence: smatsuda@cc.nara-wu.ac.jp (Satoru Matsuda)
Published: 20 April 2025

The central nervous system (CNS) and the immune system might cooperate with each other on various levels in a body. Interestingly, signaling pathways linked to several G protein-coupled receptors (GPCRs) have been shown to be involved in the pathology both of CNS disorders including neurodegenerative diseases and/or immune-related diseases. Oxidative stress and inflammation are likely to contribute to cell damage and death in these disorders, which in turn could cause mitochondrial injury. Interestingly, it has been revealed that gut microbiota could play a significant role in changing the phenotype of various neuron and/or immune-related disorders. Remarkably, GPCR signaling has been recognized as a key upstream regulator for autophagy/mitophagy via the action of the mammalian/mechanistic target of rapamycin (mTOR) signaling. In addition, adjusting the composition of gut microbiota could be applied to modulate the autophagy/mitophagy by the alteration of GPCR signaling to ameliorate the mitochondrial injury. Collectively, this approach may contribute to the innovative development of promising therapeutics for neurodegenerative diseases and/or immune-related diseases. This review describes that concept, highlighting the intracellular mTOR signaling from the cell surface GPCRs within cells of Gut-brain-immune axis.

Keywords: GPCR; mTOR; autophagy; mitophagy; gut microbiota; neurodegenerative disease; immune-related disease

Introduction

Neurodegenerative diseases are caused by the loss of neuronal cells, resulting in cognitive or motor impairments [1]. Parkinson's disease, Alzheimer's disease, Huntington's disease and Amyotrophic lateral sclerosis (ALS) are general types of these neurodegenerative diseases [2] (Fig. 1). Unfortunately, limited therapeutic options are presently available despite ongoing research efforts. The gut microbiota and its metabolites may play a substantial role in altering the functions of microglia in the brain with neurodegenerative diseases [3]. Interestingly, it has been shown that magnification of microglial activation caused by gut microbiota-derived short-chain fatty acids (SCFAs) may lead to intensified α-synuclein aggregates in the model mice of Parkinson's disease [4]. The gut-brain axis might play a key role in the development of neurodegenerative diseases through bidirectional effects of the gut and brain, which may be the intricate link for neurodegeneration. In this complicated bidirectional communication, the gut microbiota could interact with the central nervous system (CNS) via spinal nerves and/or vagus nerve [5] as well as with immune system and enteroendocrine system [6,7], which may facilitate various signal transductions in neuronal cells (Fig. 1). In addition, a lot of neurotransmitters and various metabolites produced by gut microorganisms such as gut hormones, cytokines, peptides, and neuroactive substances may also play pivotal roles in keeping this communication for the host homeostasis [8]. Therefore, the conformation of gut microbiota can affect many parts of gut and/or brain functions, including the integrity of the gut barrier, the permeability of the blood-brain barrier (BBB), the maturation of neuronal cells, and the stability of the immune system. In fact, gut dysbiosis has been shown to participate in the pathophysiology of various systemic diseases [9]. Key molecules such as neurotransmitters (dopamine, serotonin, norepinephrine, gamma-aminobutyric acid (GABA)), cytokines (interleukin (IL)-1β, IL-6, IL-10, tumor necrosis factor-α (TNF-α)), and metabolites (SCFAs, amine compounds, vitamins) can play important roles in the process of neurodegenerative disorders [10].

The precise mechanisms through which a changed gut microbiota can impact the CNS remain unclear. Here, an overview of the hypothetical mechanisms may be provided according to the identified signaling pathways linked to several G protein-coupled receptors (GPCRs). It has been shown that signaling, internalization, and desensitization of several GPCRs are involved in the pathogenesis of a variety of neurodegenerative diseases [11,12]. GPCRs have

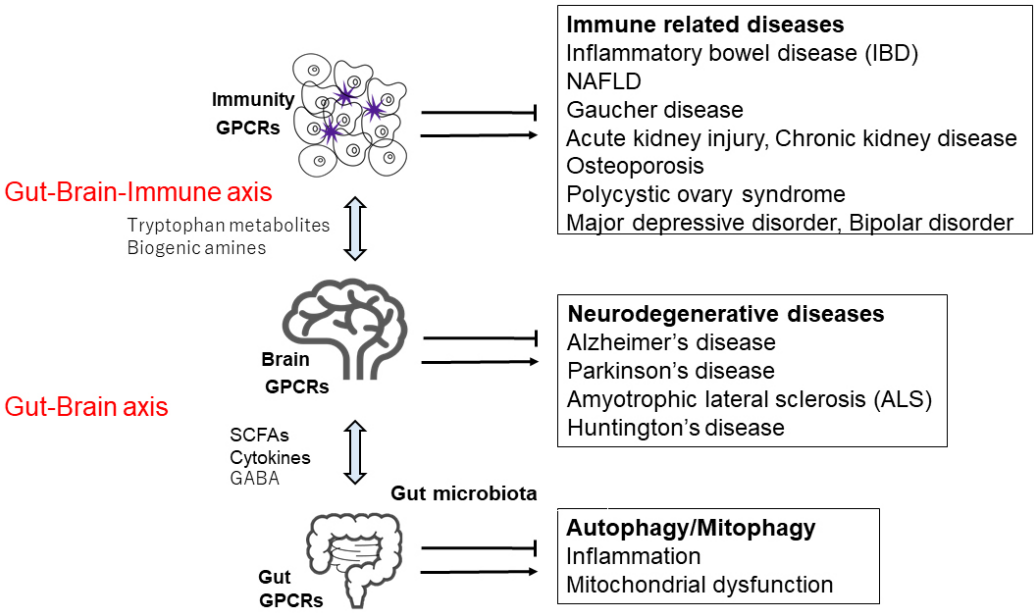

Fig. 1. Schematic representation for the development of neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, Huntington's disease, Amyotrophic lateral sclerosis (ALS), and/or immune-related diseases such as inflammatory bowel disease (IBD), Nonalcoholic fatty liver disease (NAFLD), Gaucher disease, and so on. Gut-brain-immune axis may be involved in the pathogenesis. Interestingly, G protein-coupled receptors (GPCRs) are expressed in these cells of the gut-brain-immune axis organ. The arrowhead means stimulation and/or augmentation whereas the hammerhead represents inhibition. Some critical events have been omitted for clarity. SCFAs, short-chain fatty acids; GABA, gamma-aminobutyric acid. This illustration was created using Microsoft PowerPoint 2013 (Microsoft Corporation, Redmond, WA, USA).

emerged as promising targets in the CNS, offering new avenues for drug development against neurodegenerative diseases [13]. In addition, GPCRs are deeply involved in other human diseases via the effects of a multitude of endogenous and exogenous cues [14]. For example, GPCRs are promising targets in research on new strategies for the diagnostics and/or treatment of colorectal cancer [15]. Furthermore, GPCRs can participate in immune cell recruitment and immune modulations [16]. Subsequently, it has been shown that GPCRs may be potential targets for cancer immunotherapy [17]. In these ways, GPCRs are pivotal in mediating diverse physiological and pathological processes, providing promising targets for drug discovery [18]. Here, we discuss the key role of GPCRs in various cell types for brain homeostasis, which would facilitate the study of GPCR mechanisms for accelerating the process of GPCR-targeted drug discovery against various disorders.

GPCRs Expressed in Cells of the Gut-Brain-Immune Axis

GPCRs represent membrane receptors comprising seven transmembrane helix proteins playing a vital role in various physiological and pathological processes, which comprise the largest class of receptor family in the human proteins [19,20]. There are more than 150 GPCRs, for which the natural ligands are still unknown. These orphan receptors remain unexplored in terms of their molecular signaling pathways and functions [21]. Various GPCR ligands have been recognized at present, such as prostaglandin E2, sphingosine 1-phosphate, lysophosphatidic acid, carbachol, stromal cell-derived factor, isoproterenol, follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), and luteinizing hormone (LH)/choriogonadotropin (CG), ranging from hormonal peptides, chemokines, neurotransmitters, lipids, nucleotides, amino acids, biogenic amines to ions and so forth [22]. Therefore, GPCRs could perceive a diversity of extracellular stimuli. As a result, intracellular G protein-coupled pathways may regulate many biological processes involved in normal physiological functions of the body as well as in the pathological progression of diseases [23]. Interestingly, GPCRs are selectively expressed on specific human cells including enteric, brain, and immune cells, suggesting clues to gut-brain-immune intricate interactions, which may importantly represent an opportunity to address several diseases [24,25].

Many approved drugs may target GPCRs, which are mostly expressed within the CNS. Notably, biogenic amine, endocannabinoids, and opioid receptors are key targets for treating neuropsychiatric disorders [26]. Meanwhile, astrocytes have an active structural and functional interaction with neurons at the synapse [27]. The wide variety of receptors expressed by astrocytes, including GPCRs, could be activated by neurotransmitters and other small molecules,

thereby allowing the detection of alterations in synaptic activity [28]. GPCRs are known to activate several intracellular signaling pathways hanging on their binding to G_q, inhibitory G proteins (G_i), or stimulatory G proteins (G_s) [29]. GPCR signaling in astrocytes may mainly focus on the hippocampus memories [30]. Interestingly, GPCRs in the gut enteroendocrine cells can respond to nutritional, and microbial signals, which may modulate the release of gut hormones [31]. For example, GPCRs could regulate the glucagon-like peptide-1 (GLP-1) production/secretion in entero-endocrine cells by responding to the rise of carbohydrates [32], which in turn activate downstream signaling pathways through various second messengers [33]. Understanding the biological actions of GPCRs would provide insight into developing novel diabetes therapeutics by stimulating endogenous GLP-1 discharge [25,34]. It has been suggested that the G protein-coupled orphan receptor 17 (GPR17) can contribute to the control of glucose metabolism by modifying the GLP-1 discharge [31]. In addition, SCFAs are known to play a key role in gut-brain communication [35], which have been shown to interact with some GPCRs including GPR41, GPR43, and GPR109A localized on the intestinal epithelial cells [36]. On these GPCR activations, a series of signaling actions are started, which could also have an impact on the function of the immune cells. For example, the roles of GPCR signaling can facilitate a virus entry into lymphocytes inducing immune cell handling [37,38]. Some GPCRs could also promote tumor growth and its dissemination by the alteration of the immune system [39]. The character of the immune cell infiltrating the tumor microenvironment (TME) is principally determined by chemokines and their association with GPCRs [40]. Several inflammatory mediators such as reactive oxygen species (ROS) that accumulate in the TME may act on the $G\alpha_s$-coupled receptors to exhibit an immunosuppressive activity [41]. Furthermore, GPCRs may be indispensable for the control of immune dynamics, where several immune cells could organize their behaviors during tumor immune responses.

Most immune cells may express more than one GPCR on their cell surfaces, permitting them to sense a wide range of chemo-attractants and/or chemokines in various tissues. Based on the GPCR expression patterns, immune cells can recognize the same ranges of chemo-attractants, which may control the total functionality of the immune system [42]. It has been shown that similar expression patterns of GPCRs from human intestinal epithelial cells and different brain regions to various immune cells such as dendritic cells B-cells, T-cells, natural killer cells (NK-cells), neutrophils, monocytes, and macrophages. Probably, information about all of these signaling events could be used to treat various diseases with certain diets via the alteration of the gut-brain-immune axis. Interestingly, tryptophan metabolites have been shown to diffuse through the intestinal epithelium and modulate innate and/or adaptive immune responses via the G protein-coupled orphan receptor 35 (GPR35) and 5-hydroxytryptamine receptors, also expressed in the brain neuronal cells [43]. The capacity of the gut-brain-immune axis to modulate different immune cells and inflammation-related processes including ROS production makes it a promising therapeutic target for managing immune-related diseases [44]. However, further studies are warranted to elucidate the molecular mechanisms causing their effects in the development of immune-related diseases.

GPCRs and mTOR Pathway Involved in the Regulation of Autophagy

GPCRs are crucial for regulating essential biological processes that alter cell states and pivotal targets for medication development [45,46]. These GPCRs could begin to activate heterotrimeric G proteins for the production of second messengers, stimulating several effector kinases in an extracellular stimulus-dependent manner [47]. Structurally, GPCRs share a typical architecture comprising an intracellular domain and an extracellular domain, a transmembrane domain stabilized by seven alpha helix structures, which significantly interact with G proteins including G_s, $G_{q/11}$, $G_{12/13}$, and G_i [48,49]. Remarkably, they can respond to various external stimuli such as odorants, chemokines, neurotransmitters, and ions, which could structurally change the proteins into an active position [50,51]. The phosphoinositide-3 kinase (PI3K)/protein kinase B (AKT)/mammalian/mechanistic target of rapamycin (mTOR) signaling pathway is indispensable for cell metabolism, cell survival, cell migration, and immune function, which may be administrated by cell surface GPCRs [52] (Fig. 2). In addition, stimulation of GPCRs can also regulate intracellular other signaling effectors such as phospholipases, mitogen-activated protein kinases (MAPKs), ion channels, and adenylyl/guanylyl cyclases [53,54]. For example, human serotonin can bind to the 5-hydroxytryptamine (5-HT)-GPCR, which is important for angiogenesis [54,55]. In addition, serotonin might activate dopaminergic neuron activity in a region-dependent manner through the GPCR, contributing to neurological functions [55]. Interestingly, several medicinal herbs including curcumin, danshensu, and/or puerarin have been examined to initiate neuroprotective effects via the GPCR/PI3K/AKT pathway [54]. In addition, docosahexaenoic acid (DHA) and polyunsaturated fatty acid may also influence the oligomerization of GPCRs by changing the cell membrane composition, which may be observed to increase neuronal survival by GPCR signaling [56]. In fact, the free fatty acids can increase glucose uptake via the PI3K/AKT signaling [57]. Additionally, activation of the mTOR protein kinase represents another consequential downstream process initiated by GPCR/PI3K/AKT activation. It is triggered by TSC2 phosphorylation, lead-

ing to the activation of mTORC1, a multiprotein complex. The mTORC1 could in turn drive the downstream activation of the eIF4 complex, which afterward inhibits apoptosis and regulates the cell cycle [58]. Remarkably, this PI3K/AKT/mTOR signaling has been recognized as a key upstream regulator of autophagy [59]. Similarly, it has been shown that the PI3K/AKT/mTOR signaling is also involved in the alteration of autophagy [60]. Autophagy is a fundamental component of cell-autonomous immunity, targeting intracellular pathogens including viruses and cytosolic bacteria to lysosomes for degradation. The mTOR is a serine/threonine protein kinase. As mentioned above, there are two mTOR-complexes, mTORC1 and mTORC2. The mTORC1 is considered a major negative regulator of autophagy with a major upstream modulator of the PI3K/AKT signaling pathway [61]. The function of mTORC2 might be controlling the organization of the cytoskeleton [62]. The inhibition of the GPCRs/PI3K/AKT/mTOR signaling pathway can promote autophagy, while the activation of this pathway obstructs autophagy [36]. Therefore, the dysregulation of this GPCRs/PI3K/AKT/mTOR pathway has been described in various pathologies [63]. For example, the activation of GPCRs is a crucial factor contributing to cardiac hypertrophy, in which the dysregulation of autophagy is implicated [64]. Inflammation and immune responses may play important roles in the development of cardiac hypertrophy [65]. Taken together, GPCRs could play roles in regulating the PI3K/AKT/mTOR signaling pathway associated with autophagy and potentially improve various pathologies.

GPCRs Involved in the Regulation of Neurodegenerative Diseases and Immune-Related Diseases via the Alteration of Autophagy/Mitophagy

Dysfunction of the autophagy machinery may lead to the accumulation of abnormal proteins or damaged organelles, which are linked to various human diseases such as diabetes, autoimmune diseases, cancers, and neurodegenerative diseases [66]. In addition, autophagy-related research has increasingly focused on its role in inflammation and/or immune responses. Interestingly, restoration of microglial autophagy has been shown to be critical for alleviating symptoms of neuroinflammation and/or neurodegeneration [67,68]. Mitophagy is a selective form of autophagy, devoted to degrade damaged mitochondria. As mitophagy is a crucial process for mitochondrial quality control, the failure of mitophagy could lead to the accumulation of flawed mitochondria, causing a risk of damage to energy-asking neuronal cells. Therefore, mitophagy dysfunction is a key factor in the incidence and/or progression of various neurodegenerative diseases such as ALS, Huntington's disease, Parkinson's disease, and Alzheimer's disease [69]. In general, mitophagy can play an essential role in many cellular processes, such as inflammation, apoptosis, cell differentiation and proliferation, and mitochondrial turnover, modifying mitochondrial numbers. Chronic neuro-inflammation via dysregulated immune activation triggers the accumulation of neurotoxic misfolded proteins in and around CNS cells resulting in neuronal death. The neuronal death is probably induced by the inability to control protein aggregates, mitochondrial instability, and excess oxidative stress [70]. Hence, mitochondria dynamics have been linked to many human diseases including neurodegenerative diseases [71].

A positive relationship between mitophagy rate, mitochondrial health, and individual longevity has been recognized in many model systems. Furthermore, it has been detected that mitophagy also contributes to the regulation of the immune responses. Mitophagy has the potential to exert an anti-inflammatory effect by repressing the excessive production of cytokines such as IL-1β [72]. Accordingly, the dysregulation of mitophagy could cause inflammation by stimulating the NLR family pyrin domain-containing protein 3 (NLRP3) inflammasomes, resulting in an overproduction of the IL-1β [73]. In addition, mitochondrial impairment has been shown to activate the transcription of other inflammatory factors including TNF-α [74]. Furthermore, abnormal mitophagy is connected to several autoimmune disorders, which are regulated by the association between innate and adaptive immune responses with the production of various cytokines [75]. Genetic mutations in components of the autophagy/mitophagy pathway may result in autoinflammatory and neurodegenerative disorders [76].

Interestingly, emerging evidence links gut dysbiosis to the aggravation and/or spread of proteinopathies from the peripheral nervous system to the CNS and defective autophagy-mediated proteinopathies, which contribute to the development of neurodegeneration [77]. An altered microbiome coupled with defects in autophagy can also drive chronic immune activation in a drosophila model of immune-related Gaucher disease [78] (Fig. 1). In addition, the potential targeting of the microbiota and modulating autophagic pathways have been addressed for the therapy of inflammatory bowel disease (IBD) [79]. Further studies are necessary to explore restoring microbial balance and regulating autophagy mechanisms, which may offer new therapeutic avenues for brain and/or immune management. In this regard, comprehension of GPCR function with the modification of autophagy/mitophagy would be beneficial for the development of GPCR-targeted therapeutics in the future. For instance, it has been reported that GLP-1 and/or serotonin, whose receptors are GPCRs, may play a favorable role in the treatment of Alzheimer's disease [80,81], in which GPCR signaling pathway has been shown for the modification of autophagy/mitophagy [80,81]. Therefore, certain GPCRs could regulate the pathology of neurodegenerative diseases and immune-related diseases via the modification of autophagy/mitophagy.

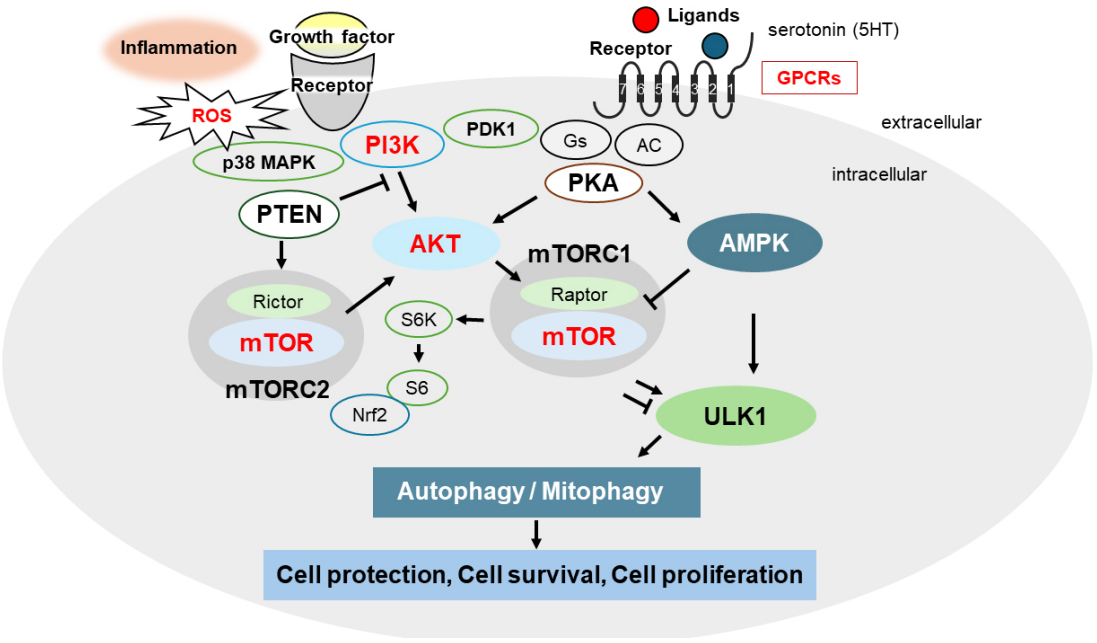

Fig. 2. An illustrative representation of the GPCR signaling pathways. Several modulator molecules associated with the receptors in their downstream pathway are also demonstrated. For example, the stimulation of serotonin (5-hydroxytryptamine (5-HT)) receptor, a GPCR, may result in the activation of the adenylyl cyclase (AC) that can transform adenosine triphosphate (ATP) into 3-5-cyclic adenosine monophosphate (cAMP), which may then activate the cAMP-dependent protein kinase (PKA) as well as the following AMPK for the alteration of autophagy and/or mitophagy. Note that some pathways critical for the development of disease-related signaling have been omitted for clarity. Arrowhead means stimulation whereas hammerhead represents inhibition. ROS, reactive oxygen species; MAPK, mitogen-activated protein kinases; AKT, protein kinase B; AMPK, adenosine monophosphate-activated protein kinase; mTOR, mammalian/mechanistic target of rapamycin; PI3K, phosphoinositide-3 kinase; PKA, protein kinase A; PTEN, Phosphatase and Tensin Homolog Deleted from Chromosome 10; PDK1, Pyruvate Dehydrogenase (Acetyl-Transferring) Kinase Isozyme 1; ULK1, Unc-51-like autophagy-activating kinases 1; AC, adenylate cyclase; G_s, stimulatory G proteins; S6, Ribosomal protein S6; S6K, Ribosomal protein S6 kinase; Nrf2, nuclear factor-erythroid 2-related factor 2. This illustration was created using Microsoft PowerPoint 2013 (Microsoft Corporation, Redmond, WA, USA).

Diet, Probiotics, and Gut-Brain-Immune Axis for the Therapeutic Implication of Several Diseases Possibly via the Modification of GPCRs Signaling Pathway

Neuroimaging techniques have been used to analyze the assembly, function, and molecular features of brain activity in healthy humans and patients, which has resulted in a comprehension of the microbiota-gut-brain axis [82]. There has been a noteworthy stream of interest encompassing the gut-brain axis due to its accepted roles in the regulation of health and the development of various diseases, as well as its latent therapeutic targets [83]. Experimental evidence underlines the deep influence of the microbiota via the gut-brain axis on neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease [84], which also underlines the key role of the gut microbiota in preserving general health [85]. The gut microbiota is involved in the regulation of mental health and/or social behaviors [86]. The crosstalk between the gut microbiota and the brain is critical in the development of neurodegenerative diseases, in which modifying the gut microbiota could hold promise as a therapeutic possibility for neurodegenerative diseases [87]. Remarkably, it has been shown that the gut microbiome has the potential to control brain functions through the immunological pathway and lymphatic circulation [88]. The relationship between gut microbiota and neurological diseases has become a key focus of recent research.

The human gut microbiome plays a crucial role in regulating systemic health, impacting host immune responses. Therefore, dysbiosis of the gut microbiome is linked to various immune-related diseases including steatotic liver diseases [89]. Gut dysbiosis can trigger inflammation and metabolic dysfunction, which are intensely associated with diabetes, IBD, and/or cancers [90,91]. The gut microbiota could affect disease progression by regulating the host's immune responses either directly or indirectly [92]. Therefore, alterations in the composition of gut microbes may have potential applications in the diagnosis and/or treatment of these diseases [93]. For the application of this to the immune system, it has been revealed that certain gut microbiota could play an integral role in optimal im-

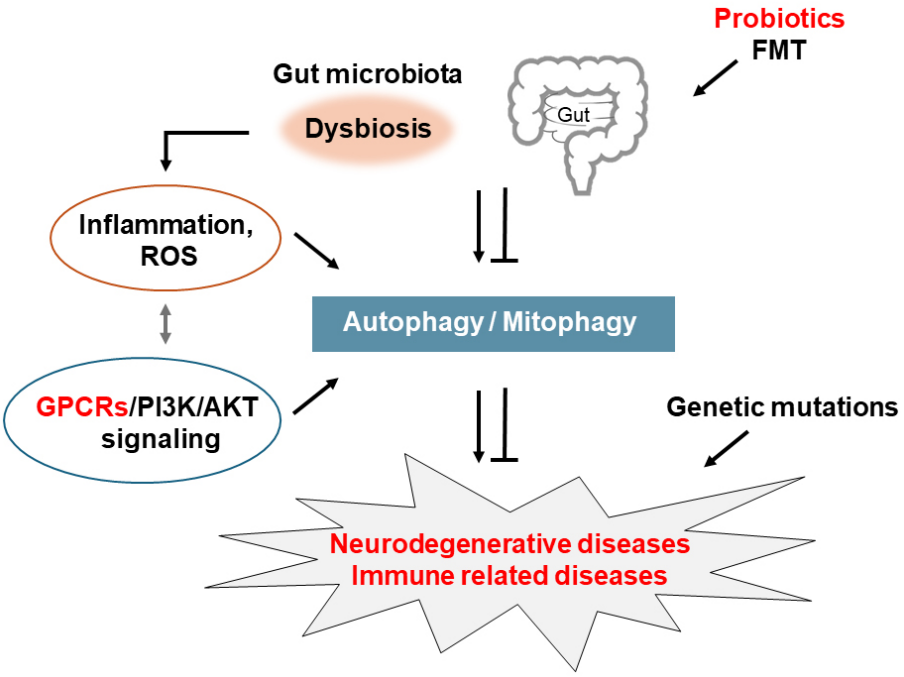

Fig. 3. Potential tactics of several probiotics and/or fecal microbiota transplantation (FMT) against the pathology of neurodegenerative diseases and/or immune-related diseases have been shown. Probiotics and/or FMT could cause the alteration of gut microbiota, which might be beneficial for the function of autophagy/mitophagy. Improved autophagy/mitophagy may be helpful for the treatment of neurodegenerative diseases and/or immune-related diseases. Note that several significant events such as inflammatory reaction, and reactive oxygen species (ROS) production have been omitted for clarity. Stimulatory effects are indicated with arrows; inhibitory effects with hammerhead. This illustration was created using Microsoft PowerPoint 2013 (Microsoft Corporation, Redmond, WA, USA).

mune function for the treatment of immune-related diseases and/or cancers, which is a dynamic component of the multidirectional communication among gut, brain, and immune system, known as gut-brain-immune axis [94–96]. In particular, probiotics and/or the relevant diet can induce preventative and therapeutic effects for these diseases [82,97] (Fig. 3). Probiotics are live microorganisms that can deliver health benefits to their hosts by administration within appropriate amounts [98]. Probiotics have been broadly used in the pharmaceutical and medical areas for years [99]. Dietary intake of probiotics may be in the form of several products such as yogurt, some beverages, and supplements [100]. For instance, probiotic species such as *Lactobacillus Casei*, and *Bifidobacterium Lactis* have been used by humans [101]. These probiotics may support immunity and improve symptoms of immune-related diseases and/or cancers [102]. It has been shown that certain probiotics could reduce the risk of colorectal cancer and inhibit tumor growth [103]. In these ways, probiotics have a wide range of human health benefits. Interestingly, it has been revealed that probiotic therapy may be applied to modulate the function of GPCRs to ameliorate liver metabolism syndrome [104]. Nonalcoholic fatty liver disease (NAFLD) patients with progressive liver fibrosis have a prevalence of developing cirrhosis and hepatocellular carcinoma [105]. GPCRs and their signaling pathways are promising targets for NAFLD treatment [104]. In addition, oral administration of probiotics can ameliorate chronic metabolic inflammation in NAFLD model rats via the alteration of the GPR43 signaling pathway [106].

Future Perspectives

The CNS and the immune system might cooperate on various levels in a body. However, the mechanisms of holding the specific immune challenge have remained vague. There are several advantages to targeting GPCRs to treat neurodegenerative diseases and immune-related diseases compared with other therapeutics. Therapeutic candidate drugs may be effortlessly found. About one-third of Food and Drug Administration-approved drugs may target various GPCRs [21,107]. GPCRs are involved in the development and/or progression of various disorders including inflammation, metabolism, and cell proliferation. However, current GPCRs-mediated treatments in diseases are mainly achieved either in *in-vitro* cells or *in-vivo* animals. Further research is desirable to reveal the role of GPCRs in clinical settings. For example, a more comprehensive understanding of the molecular mechanisms that can regulate GPCR expression has a great deal of potential therapeutic significance. In particular, the predicted gut microbiota-GPCRs interaction may shed insight into further promis-

ing validations. Although the precise pathogenesis of neurodegenerative diseases remains unclear, some clues of the pathology have been shown to be associated with the abnormal accumulation of aggregation proteins such as the alpha-synuclein and the tau protein in Parkinson's disease and Alzheimer's disease respectively [108]. Several GPCRs signaling within CNS cells might participate in the modification of autophagy, which could remove these pathological proteins via the action of autophagy [109]. Interestingly, it has been shown that several GPCRs can play integral roles in Alzheimer's disease pathogenesis [110]. In addition, GPCRs-targeted therapies for neurodegenerative diseases have been suggested as candidate therapeutics [111]. Cutting-edge technologies may help resolve the distinct role of each GPCR in both physiological and pathological stages to accelerate GPCR-mediated therapies.

Conclusions

Several GPCR signaling pathways are involved in the regulation of autophagy/mitophagy. Alteration of the autophagy/mitophagy could regulate the pathology of neurodegenerative diseases and immune-related diseases. Therefore, certain GPCRs signaling with their respective ligands could be beneficial for the treatment of neurodegenerative diseases and/or immune-related diseases via the modification of autophagy/mitophagy. Probiotics and/or fecal microbiota transplantation (FMT) could cause the alteration of gut microbiota, which might be beneficial for the modification of autophagy/mitophagy.

Author Contributions

Conceptualization, AF, NS, MN, and SM; original draft preparation and editing, AF, and SM; visualization, AF and SM; supervision, SM. Each author has participated sufficiently in this work of drafting the article and/or revising the article for the important rational content. Then, all authors gave final approval of the version to be submitted. Finally, all authors have read and agreed to the published version of the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Ramanan VK, Saykin AJ. Pathways to neurodegeneration: mechanistic insights from GWAS in Alzheimer's disease, Parkinson's disease, and related disorders. American Journal of Neurodegenerative Disease. 2013; 2: 145–175.

[2] Ma YY, Li X, Yu JT, Wang YJ. Therapeutics for neurodegenerative diseases by targeting the gut microbiome: from bench to bedside. Translational Neurodegeneration. 2024; 13: 12.

[3] Zhang Y, Shen Y, Liufu N, Liu L, Li W, Shi Z, *et al*. Transmission of Alzheimer's disease-associated microbiota dysbiosis and its impact on cognitive function: evidence from mice and patients. Molecular Psychiatry. 2023; 28: 4421–4437.

[4] Sampson TR, Debelius JW, Thron T, Janssen S, Shastri GG, Ilhan ZE, *et al*. Gut Microbiota Regulate Motor Deficits and Neuroinflammation in a Model of Parkinson's Disease. Cell. 2016; 167: 1469–1480.e12.

[5] Hyland NP, Cryan JF. Microbe-host interactions: Influence of the gut microbiota on the enteric nervous system. Developmental Biology. 2016; 417: 182–187.

[6] Yoo JY, Groer M, Dutra SVO, Sarkar A, McSkimming DI. Gut Microbiota and Immune System Interactions. Microorganisms. 2020; 8: 1587.

[7] Yu Y, Yang W, Li Y, Cong Y. Enteroendocrine Cells: Sensing Gut Microbiota and Regulating Inflammatory Bowel Diseases. Inflammatory Bowel Diseases. 2020; 26: 11–20.

[8] Fung TC, Olson CA, Hsiao EY. Interactions between the microbiota, immune and nervous systems in health and disease. Nature Neuroscience. 2017; 20: 145–155.

[9] Matacchione G, Piacenza F, Pimpini L, Rosati Y, Marcozzi S. The role of the gut microbiota in the onset and progression of heart failure: insights into epigenetic mechanisms and aging. Clinical Epigenetics. 2024; 16: 175.

[10] Zheng Y, Bonfili L, Wei T, Eleuteri AM. Understanding the Gut-Brain Axis and Its Therapeutic Implications for Neurodegenerative Disorders. Nutrients. 2023; 15: 4631.

[11] Öz-Arslan D, Yavuz M, Kan B. Exploring orphan GPCRs in neurodegenerative diseases. Frontiers in Pharmacology. 2024; 15: 1394516.

[12] Kee TR, Khan SA, Neidhart MB, Masters BM, Zhao VK, Kim YK, *et al*. The multifaceted functions of β-arrestins and their therapeutic potential in neurodegenerative diseases. Experimental & Molecular Medicine. 2024; 56: 129–141.

[13] Kim J, Choi C. Orphan GPCRs in Neurodegenerative Disorders: Integrating Structural Biology and Drug Discovery Approaches. Current Issues in Molecular Biology. 2024; 46: 11646–11664.

[14] Calebiro D, Miljus T, O'Brien S. Endomembrane GPCR signaling: 15 years on, the quest continues. Trends in Biochemical Sciences. 2025; 50: 46–60.

[15] Swierczynski M, Kasprzak Z, Makaro A, Salaga M. Regulators of G-Protein Signaling (RGS) in Sporadic and Colitis-Associated Colorectal Cancer. International Journal of Molecular Sciences. 2024; 25: 577.

[16] Zheng K, Chen M, Xu X, Li P, Yin C, Wang J, *et al*. Chemokine CXCL13-CXCR5 signaling in neuroinflammation and pathogenesis of chronic pain and neurological diseases. Cellular & Molecular Biology Letters. 2024; 29: 134.

[17] Qiu GH, Yu B, Ma M. G protein-coupled receptor-mediated signaling of immunomodulation in tumor progression. FASEB Journal. 2024; 38: e23829.

[18] Yang H, Wang Y, Liu W, He T, Liao J, Qian Z, *et al*. Genome-

wide pan-GPCR cell libraries accelerate drug discovery. Acta Pharmaceutica Sinica. B. 2024; 14: 4296–4311.

[19] Lee Y, Basith S, Choi S. Recent Advances in Structure-Based Drug Design Targeting Class A G Protein-Coupled Receptors Utilizing Crystal Structures and Computational Simulations. Journal of Medicinal Chemistry. 2018; 61: 1–46.

[20] Spillantini MG, Schmidt ML, Lee VM, Trojanowski JQ, Jakes R, Goedert M. Alpha-synuclein in Lewy bodies. Nature. 1997; 388: 839–840.

[21] Sriram K, Insel PA. G Protein-Coupled Receptors as Targets for Approved Drugs: How Many Targets and How Many Drugs? Molecular Pharmacology. 2018; 93: 251–258.

[22] Law NC, White MF, Hunzicker-Dunn ME. G protein-coupled receptors (GPCRs) That Signal via Protein Kinase A (PKA) Cross-talk at Insulin Receptor Substrate 1 (IRS1) to Activate the phosphatidylinositol 3-kinase (PI3K)/AKT Pathway. The Journal of Biological Chemistry. 2016; 291: 27160–27169.

[23] Wang K, Wong YH. G protein signaling controls the differentiation of multiple cell lineages. BioFactors. 2009; 35: 232–238.

[24] Ehrlich AT, Maroteaux G, Robe A, Venteo L, Nasseef MT, van Kempen LC, *et al*. Expression map of 78 brain-expressed mouse orphan GPCRs provides a translational resource for neuropsychiatric research. Communications Biology. 2018; 1: 102.

[25] Hauser AS, Attwood MM, Rask-Andersen M, Schiöth HB, Gloriam DE. Trends in GPCR drug discovery: new agents, targets and indications. Nature Reviews. Drug Discovery. 2017; 16: 829–842.

[26] Anversa RG, Maddern XJ, Lawrence AJ, Walker LC. Orphan peptide and G protein-coupled receptor signalling in alcohol use disorder. British Journal of Pharmacology. 2024; 181: 595–609.

[27] Badia-Soteras A, Octeau JC, Verheijen MHG, Khakh BS. Assessing Neuron-Astrocyte Spatial Interactions Using the Neuron-Astrocyte Proximity Assay. Current Protocols in Neuroscience. 2020; 91: e91.

[28] Kofuji P, Araque A. G-Protein-Coupled Receptors in Astrocyte-Neuron Communication. Neuroscience. 2021; 456: 71–84.

[29] Lee SH, Mak A, Verheijen MHG. Comparative assessment of the effects of DREADDs and endogenously expressed GPCRs in hippocampal astrocytes on synaptic activity and memory. Frontiers in Cellular Neuroscience. 2023; 17: 1159756.

[30] Roh WS, Yoo JH, Dravid SM, Mannaioni G, Krizman EN, Wahl P, *et al*. Astrocytic PAR1 and mGluR2/3 control synaptic glutamate time course at hippocampal CA1 synapses. Glia. 2024; 72: 1707–1724.

[31] Yan S, Conley JM, Reilly AM, Stull ND, Abhyankar SD, Ericsson AC, *et al*. Intestinal Gpr17 deficiency improves glucose metabolism by promoting GLP-1 secretion. Cell Reports. 2022; 38: 110179.

[32] Reimann F, Tolhurst G, Gribble FM. G-protein-coupled receptors in intestinal chemosensation. Cell Metabolism. 2012; 15: 421–431.

[33] Ezcurra M, Reimann F, Gribble FM, Emery E. Molecular mechanisms of incretin hormone secretion. Current Opinion in Pharmacology. 2013; 13: 922–927.

[34] Sangwung P, Ho JD, Siddall T, Lin J, Tomas A, Jones B, *et al*. Class B1 GPCRs: insights into multireceptor pharmacology for the treatment of metabolic disease. American Journal of Physiology. Endocrinology and Metabolism. 2024; 327: E600–E615.

[35] Krautkramer KA, Fan J, Bäckhed F. Gut microbial metabolites as multi-kingdom intermediates. Nature Reviews. Microbiology. 2021; 19: 77–94.

[36] Dalile B, Van Oudenhove L, Vervliet B, Verbeke K. The role of short-chain fatty acids in microbiota-gut-brain communication. Nature Reviews. Gastroenterology & Hepatology. 2019; 16: 461–478.

[37] Colin P, Bénureau Y, Staropoli I, Wang Y, Gonzalez N, Alcami J, *et al*. HIV-1 exploits CCR5 conformational heterogeneity to escape inhibition by chemokines. Proceedings of the National Academy of Sciences of the United States of America. 2013; 110: 9475–9480.

[38] Schumann K, Lämmermann T, Bruckner M, Legler DF, Polleux J, Spatz JP, *et al*. Immobilized chemokine fields and soluble chemokine gradients cooperatively shape migration patterns of dendritic cells. Immunity. 2010; 32: 703–713.

[39] Wang X, Jespers W, Bongers BJ, Habben Jansen MCC, Stangenberger CM, Dilweg MA, *et al*. Characterization of cancer-related somatic mutations in the adenosine A_{2B} receptor. European Journal of Pharmacology. 2020; 880: 173126.

[40] Wu V, Yeerna H, Nohata N, Chiou J, Harismendy O, Raimondi F, *et al*. Illuminating the Onco-GPCRome: Novel G protein-coupled receptor-driven oncocrine networks and targets for cancer immunotherapy. The Journal of Biological Chemistry. 2019; 294: 11062–11086.

[41] Vigano S, Alatzoglou D, Irving M, Ménétrier-Caux C, Caux C, Romero P, *et al*. Targeting Adenosine in Cancer Immunotherapy to Enhance T-Cell Function. Frontiers in Immunology. 2019; 10: 925.

[42] Lämmermann T, Kastenmüller W. Concepts of GPCR-controlled navigation in the immune system. Immunological Reviews. 2019; 289: 205–231.

[43] Agus A, Planchais J, Sokol H. Gut Microbiota Regulation of Tryptophan Metabolism in Health and Disease. Cell Host & Microbe. 2018; 23: 716–724.

[44] Petkova H, Simic M, Nicholls D, Ford T, Prina AM, Stuart R, *et al*. Incidence of anorexia nervosa in young people in the UK and Ireland: a national surveillance study. BMJ Open. 2019; 9: e027339.

[45] Neasta J, Darcq E, Jeanblanc J, Carnicella S, Ben Hamida S. GPCR and Alcohol-Related Behaviors in Genetically Modified Mice. Neurotherapeutics. 2020; 17: 17–42.

[46] De Deurwaerdère P, Ponimaskin E, Chagraoui A, Di Giovanni G. Editorial: New GPCR targets and modulators to treat CNS disorders. Frontiers in Molecular Neuroscience. 2022; 15: 1104336.

[47] Young Yang M, Duy Mac K, Strzelinski HR, Hoffman SA, Kim D, Kim SK, *et al*. Agonist activation to open the Gα subunit of the GPCR-G protein precoupled complex defines functional agonist activation of TAS2R5. Proceedings of the National Academy of Sciences of the United States of America. 2024; 121: e2409987121.

[48] Lappano R, Jacquot Y, Maggiolini M. GPCR Modulation in Breast Cancer. International Journal of Molecular Sciences. 2018; 19: 3840.

[49] Ritter SL, Hall RA. Fine-tuning of GPCR activity by receptor-interacting proteins. Nature Reviews. Molecular Cell Biology. 2009; 10: 819–830.

[50] Neves SR, Ram PT, Iyengar R. G protein pathways. Science. 2002; 296: 1636–1639.

[51] Audet M, Bouvier M. Restructuring G-protein- coupled receptor activation. Cell. 2012; 151: 14–23.

[52] Coso OA, Chiariello M, Yu JC, Teramoto H, Crespo P, Xu N, *et al*. The small GTP-binding proteins Rac1 and Cdc42 regulate the activity of the JNK/SAPK signaling pathway. Cell. 1995; 81: 1137–1146.

[53] New DC, Wu K, Kwok AWS, Wong YH. G protein-coupled receptor-induced Akt activity in cellular proliferation and apoptosis. The FEBS Journal. 2007; 274: 6025–6036.

[54] Nakano N, Matsuda S, Ichimura M, Minami A, Ogino M, Murai T, *et al*. PI3K/AKT signaling mediated by G protein coupled receptors is involved in neurodegenerative Parkinson's disease (Review). International Journal of Molecular Medicine. 2017; 39: 253–260.

[55] Zamani A, Qu Z. Serotonin activates angiogenic phosphorylation signaling in human endothelial cells. FEBS Letters. 2012; 586: 2360–2365.
[56] Guixà-González R, Javanainen M, Gómez-Soler M, Cordobilla B, Domingo JC, Sanz F, *et al*. Membrane omega-3 fatty acids modulate the oligomerisation kinetics of adenosine A2A and dopamine D2 receptors. Scientific Reports. 2016; 6: 19839.
[57] Pu J, Liu P. Fatty acids stimulate glucose uptake by the PI3K/AMPK/Akt and PI3K/ERK1/2 pathways. Protein Phosphorylation in Human Health. 2012; 129: 52456.
[58] Engelman JA, Luo J, Cantley LC. The evolution of phosphatidylinositol 3-kinases as regulators of growth and metabolism. Nature Reviews. Genetics. 2006; 7: 606–619.
[59] Li J, Jiang M, Yu Z, Xiong C, Pan J, Cai Z, *et al*. Artemisinin relieves osteoarthritis by activating mitochondrial autophagy through reducing TNFSF11 expression and inhibiting PI3K/AKT/mTOR signaling in cartilage. Cellular & Molecular Biology Letters. 2022; 27: 62.
[60] Yang CZ, Wang SH, Zhang RH, Lin JH, Tian YH, Yang YQ, *et al*. Neuroprotective effect of astragalin via activating PI3K/Akt-mTOR-mediated autophagy on APP/PS1 mice. Cell Death Discovery. 2023; 9: 15.
[61] Alzahrani AS. PI3K/Akt/mTOR inhibitors in cancer: At the bench and bedside. Seminars in Cancer Biology. 2019; 59: 125–132.
[62] Xu W, Hua H, Chiu YH, Li G, Zhi H, Yu Z, *et al*. CD146 Regulates Growth Factor-Induced mTORC2 Activity Independent of the PI3K and mTORC1 Pathways. Cell Reports. 2019; 29: 1311–1322.e5.
[63] Heras-Sandoval D, Pérez-Rojas JM, Hernández-Damián J, Pedraza-Chaverri J. The role of PI3K/AKT/mTOR pathway in the modulation of autophagy and the clearance of protein aggregates in neurodegeneration. Cellular Signalling. 2014; 26: 2694–2701.
[64] Liu Y, Zhang H, Lin Y, Qian P, Yin Y, Zou G, *et al*. Deficiency of diacylglycerol Kinase ζ promotes Beclin1-mediated autophagy *via* the mTOR/TFEB signaling pathway: Relevance to maladaptive cardiac hypertrophy. International Journal of Medical Sciences. 2024; 21: 439–453.
[65] Du BB, Shi HT, Xiao LL, Li YP, Yao R, Liang C, *et al*. Melanoma differentiation-associated protein 5 prevents cardiac hypertrophy via apoptosis signal-regulating kinase 1-c-Jun N-terminal kinase/p38 signaling. International Journal of Biological Macromolecules. 2024; 264: 130542.
[66] Choi AMK, Ryter SW, Levine B. Autophagy in human health and disease. The New England Journal of Medicine. 2013; 368: 1845–1846.
[67] Berglund R, Guerreiro-Cacais AO, Adzemovic MZ, Zeitelhofer M, Lund H, Ewing E, *et al*. Microglial autophagy-associated phagocytosis is essential for recovery from neuroinflammation. Science Immunology. 2020; 5: eabb5077.
[68] Plaza-Zabala A, Sierra-Torre V, Sierra A. Autophagy and Microglia: Novel Partners in Neurodegeneration and Aging. International Journal of Molecular Sciences. 2017; 18: 598.
[69] Li X, Huang L, Lan J, Feng X, Li P, Wu L, *et al*. Molecular mechanisms of mitophagy and its roles in neurodegenerative diseases. Pharmacological Research. 2021; 163: 105240.
[70] Serio A, Patani R. Concise Review: The Cellular Conspiracy of Amyotrophic Lateral Sclerosis. Stem Cells. 2018; 36: 293–303.
[71] Monzio Compagnoni G, Di Fonzo A, Corti S, Comi GP, Bresolin N, Masliah E. The Role of Mitochondria in Neurodegenerative Diseases: the Lesson from Alzheimer's Disease and Parkinson's Disease. Molecular Neurobiology. 2020; 57: 2959–2980.
[72] Xu Y, Shen J, Ran Z. Emerging views of mitophagy in immunity and autoimmune diseases. Autophagy. 2020; 16: 3–17.
[73] Zhou R, Yazdi AS, Menu P, Tschopp J. A role for mitochondria in NLRP3 inflammasome activation. Nature. 2011; 469: 221–225.
[74] Oka T, Hikoso S, Yamaguchi O, Taneike M, Takeda T, Tamai T, *et al*. Mitochondrial DNA that escapes from autophagy causes inflammation and heart failure. Nature. 2012; 485: 251–255.
[75] Al-Kuraishy HM, Sulaiman GM, Jabir MS, Mohammed HA, Al-Gareeb AI, Albukhaty S, *et al*. Defective autophagy and autophagy activators in myasthenia gravis: a rare entity and unusual scenario. Autophagy. 2024; 20: 1473–1482.
[76] Sabli IK, Sancho-Shimizu V. Inborn errors of autophagy and infectious diseases. Current Opinion in Immunology. 2021; 72: 272–276.
[77] Chidambaram SB, Essa MM, Rathipriya AG, Bishir M, Ray B, Mahalakshmi AM, *et al*. Gut dysbiosis, defective autophagy and altered immune responses in neurodegenerative diseases: Tales of a vicious cycle. Pharmacology & Therapeutics. 2022; 231: 107988.
[78] Atilano ML, Hull A, Romila CA, Adams ML, Wildfire J, Ureña E, *et al*. Autophagic dysfunction and gut microbiota dysbiosis cause chronic immune activation in a Drosophila model of Gaucher disease. PLoS Genetics. 2023; 19: e1011063.
[79] Subramanian A, Jahabardeen A, Thamaraikani T, Vellapandian C. More on the interplay between gut microbiota, autophagy, and inflammatory bowel disease is needed. World Journal of Gastroenterology. 2024; 30: 3356–3360.
[80] Nakashima M, Suga N, Yoshikawa S, Matsuda S. Caveolae with GLP-1 and NMDA Receptors as Crossfire Points for the Innovative Treatment of Cognitive Dysfunction Associated with Neurodegenerative Diseases. Molecules. 2024; 29: 3922.
[81] Nakashima M, Suga N, Fukumoto A, Yoshikawa S, Matsuda S. Caveolae with serotonin and NMDA receptors as promising targets for the treatment of Alzheimer's disease. International Journal of Physiology, Pathophysiology and Pharmacology. 2024; 16: 96–110.
[82] Liu P, Peng G, Zhang N, Wang B, Luo B. Crosstalk Between the Gut Microbiota and the Brain: An Update on Neuroimaging Findings. Frontiers in Neurology. 2019; 10: 883.
[83] Ghezzi L, Cantoni C, Rotondo E, Galimberti D. The Gut Microbiome-Brain Crosstalk in Neurodegenerative Diseases. Biomedicines. 2022; 10: 1486.
[84] Szandruk-Bender M, Wiatrak B, Szeląg A. The Risk of Developing Alzheimer's Disease and Parkinson's Disease in Patients with Inflammatory Bowel Disease: A Meta-Analysis. Journal of Clinical Medicine. 2022; 11: 3704.
[85] Ross FC, Mayer DE, Gupta A, Gill CIR, Del Rio D, Cryan JF, *et al*. Existing and Future Strategies to Manipulate the Gut Microbiota With Diet as a Potential Adjuvant Treatment for Psychiatric Disorders. Biological Psychiatry. 2024; 95: 348–360.
[86] Ritz NL, Brocka M, Butler MI, Cowan CSM, Barrera-Bugueño C, Turkington CJR, *et al*. Social anxiety disorder-associated gut microbiota increases social fear. Proceedings of the National Academy of Sciences of the United States of America. 2024; 121: e2308706120.
[87] Zhang T, Gao G, Kwok LY, Sun Z. Gut microbiome-targeted therapies for Alzheimer's disease. Gut Microbes. 2023; 15: 2271613.
[88] Shandilya S, Kumar S, Kumar Jha N, Kumar Kesari K, Ruokolainen J. Interplay of gut microbiota and oxidative stress: Perspective on neurodegeneration and neuroprotection. Journal of Advanced Research. 2021; 38: 223–244.
[89] Meadows V, Antonio JM, Ferraris RP, Gao N. Ruminococcus gnavus in the gut: driver, contributor, or innocent bystander in steatotic liver disease? The FEBS Journal. 2024; e17327.
[90] Yu D, Meng X, de Vos WM, Wu H, Fang X, Maiti AK. Implications of Gut Microbiota in Complex Human Diseases. International Journal of Molecular Sciences. 2021; 22: 12661.

[91] Xue K, Li J, Huang R. The immunoregulatory role of gut microbiota in the incidence, progression, and therapy of breast cancer. Frontiers in Cellular and Infection Microbiology. 2024; 14: 1411249.

[92] Zhang H, Wang Y, Chen H. Role and mechanism of gut microbiota involved in host immune response. Acta Microbiologica Sinica. 2020; 60: 629–640.

[93] Zhang Y, Wang H, Sang Y, Liu M, Wang Q, Yang H, *et al*. Gut microbiota in health and disease: advances and future prospects. MedComm. 2024; 5: e70012.

[94] Yoshikawa S, Taniguchi K, Sawamura H, Ikeda Y, Tsuji A, Matsuda S. Encouraging probiotics for the prevention and treatment of immune-related adverse events in novel immunotherapies against malignant glioma. Exploration of Targeted Anti-Tumor Therapy. 2022; 3: 817–827.

[95] Yoshikawa S, Taniguchi K, Sawamura H, Ikeda Y, Asai T, Tsuji A, *et al*. Potential tactics with certain gut microbiota for the treatment of unresectable hepatocellular carcinoma. Exploration of Targeted Anti-Tumor Therapy. 2023; 4: 556–568.

[96] Tsuji A, Ikeda Y, Yoshikawa S, Taniguchi K, Sawamura H, Morikawa S, *et al*. The Tryptophan and Kynurenine Pathway Involved in the Development of Immune-Related Diseases. International Journal of Molecular Sciences. 2023; 24: 5742.

[97] Yao L, Yang Y, Yang X, Rezaei MJ. The Interaction Between Nutraceuticals and Gut Microbiota: a Novel Therapeutic Approach to Prevent and Treatment Parkinson's Disease. Molecular Neurobiology. 2024; 61: 9078–9109.

[98] Latif A, Shehzad A, Niazi S, Zahid A, Ashraf W, Iqbal MW, *et al*. Probiotics: mechanism of action, health benefits and their application in food industries. Frontiers in Microbiology. 2023; 14: 1216674.

[99] Vera-Santander VE, Hernández-Figueroa RH, Jiménez-Munguía MT, Mani-López E, López-Malo A. Health Benefits of Consuming Foods with Bacterial Probiotics, Postbiotics, and Their Metabolites: A Review. Molecules. 2023; 28: 1230.

[100] Szydłowska A, Sionek B. Probiotics and Postbiotics as the Functional Food Components Affecting the Immune Response. Microorganisms. 2022; 11: 104.

[101] Romero J, Albertos I, Díez-Méndez A, Poveda J. Control of postharvest diseases in berries through edible coatings and bacterial probiotics. Scientia Horticulturae. 2022; 304: 111326.

[102] Petrariu OA, Barbu IC, Niculescu AG, Constantin M, Grigore GA, Cristian RE, *et al*. Role of probiotics in managing various human diseases, from oral pathology to cancer and gastrointestinal diseases. Frontiers in Microbiology. 2024; 14: 1296447.

[103] Molska M, Reguła J. Potential Mechanisms of Probiotics Action in the Prevention and Treatment of Colorectal Cancer. Nutrients. 2019; 11: 2453.

[104] Yang M, Zhang CY. G protein-coupled receptors as potential targets for nonalcoholic fatty liver disease treatment. World Journal of Gastroenterology. 2021; 27: 677–691.

[105] Friedman SL, Neuschwander-Tetri BA, Rinella M, Sanyal AJ. Mechanisms of NAFLD development and therapeutic strategies. Nature Medicine. 2018; 24: 908–922.

[106] Liang Y, Liang S, Zhang Y, Deng Y, He Y, Chen Y, *et al*. Oral Administration of Compound Probiotics Ameliorates HFD-Induced Gut Microbe Dysbiosis and Chronic Metabolic Inflammation via the G Protein-Coupled Receptor 43 in Non-alcoholic Fatty Liver Disease Rats. Probiotics and Antimicrobial Proteins. 2019; 11: 175–185.

[107] Liccardo F, Morstein J, Lin TY, Pampel J, Lang D, Shokat KM, *et al*. Subcellular activation of β-adrenergic receptors using a spatially restricted antagonist. Proceedings of the National Academy of Sciences of the United States of America. 2024; 121: e2404243121.

[108] Cehlar O, Njemoga S, Horvath M, Cizmazia E, Bednarikova Z, Barrera EE. Structures of Oligomeric States of Tau Protein, Amyloid-β, α-Synuclein and Prion Protein Implicated in Alzheimer's Disease, Parkinson's Disease and Prionopathies. International Journal of Molecular Sciences. 2024; 25: 13049.

[109] Kakoty V, Kc S, Kumari S, Yang CH, Dubey SK, Sahebkar A, *et al*. Brain insulin resistance linked Alzheimer's and Parkinson's disease pathology: An undying implication of epigenetic and autophagy modulation. Inflammopharmacology. 2023; 31: 699–716.

[110] Woo JA, Yan Y, Kee TR, Cazzaro S, McGill Percy KC, Wang X, *et al*. β-arrestin1 promotes tauopathy by transducing GPCR signaling, disrupting microtubules and autophagy. Life Science Alliance. 2021; 5: e202101183.

[111] Wang XX, Ji X, Lin J, Wong IN, Lo HH, Wang J, *et al*. GPCR-mediated natural products and compounds: Potential therapeutic targets for the treatment of neurological diseases. Pharmacological Research. 2024; 208: 107395.