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The Role of Gut-Brain Axis in Modulating the Impact of Sterile Inflammation on Neuroimmune Responses in Neurodegenerative Diseases: Alzheimer's Disease and Parkinson's Disease

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Keywords

Alzheimer's disease · Gut microbiota · Microglia · Neurodegeneration · Neuroinflammation · Oxidative stress · Parkinson's disease · Prebiotics · Systemic inflammation

Abstract

Background: Emerging evidence has demonstrated the important role of gut microbiota in host physiology, affecting host immunity. The gut-brain axis has been identified between the central nervous system and the gut microbiota, indicating bidirectional communication between the two systems. ***Summary:*** Microbial imbalance (in other words, gut dysbiosis) can lead to chronic systemic inflammation, resulting in neuroinflammation as an example of sterile inflammation. Three major pathways in causing neuroinflammation from chronic systemic inflammation by the gut microbiota via the gut-brain axis are discussed throughout the article. This includes the inflammasome signaling, altered permeability of the blood-brain barrier by the short-chain fatty acids, and oxidative stress. ***Key Messages:*** Through understanding that gut dysbiosis is capable of modulating neuroinflammation, the use of probiotics in neurodegenerative diseases can be investigated to assess their therapeutic potential. Increasing clinical studies show positive results on the use of probiotics in neurodegenerative diseases, yet further evidence is required to validate their clinical effectiveness.

Introduction

Sterile Inflammation and Neurodegenerative Diseases

Inflammation is a common immune response frequently experienced during tissue repair and infection with four classical signs of redness, heat, swelling, and pain [1]. Cerebral cellular damage can lead to sterile inflammation independent of the presence of

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microorganisms, leading to neuroinflammation. Chronic neuroinflammation can result in the development of neurodegenerative diseases [2, 3]. In the face of an aging population, the world is experiencing an expanding burden of neurodegenerative diseases [4, 5], raising global concerns as there is no cure identified for these conditions currently [6]. They are characterized by protein aggregations, which can cause cell injury, causing sterile inflammation within the central nervous system (CNS) [1]. Alzheimer's disease (AD) [7] and Parkinson's disease (PD) [8] are common examples of neurodegenerative diseases that involve the aggregation of amyloid-beta (Aβ) plaques. The buildup of insoluble plaques and inclusion bodies within the brain results in the gradual dysfunction and damage of neural tissues [9]. Chronic activation and dysfunction of glial cells are one of the major contributors to neurodegenerative diseases [10]. However, the exact understanding of the pathophysiology of neurodegenerative disorders remains incomplete, which prevents the use of effective medications that can target the disease specifically [11].

Particles that are not deemed to be harmful to the host can act as an exogenous trigger, stimulating an inflammatory response [2]. Injured or necrotic tissues release endogenous molecules damage-associated molecular proteins (DAMPs) [12], such as the high-mobility group box 1 (HMGB1) proteins. These molecules are recognized by host inflammatory signaling receptors, for instance, the nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) and Toll-like receptors [2]. This is followed by an inflammatory response, which includes the production and release of proinflammatory cytokines and chemokines [13]. For example, interleukin-1 alpha (IL-1α) released by necrotic cells recruits neutrophils to the damaged site [13]. Neutrophils can release various signaling molecules to attract macrophages [2]. During an acute sterile inflammatory response, infiltrating neutrophils can exacerbate cellular damage, forming a loop between inflammation and tissue injury. This process has been demonstrated to play a significant role in the innate-immune activation in neurodegenerative diseases such as PD and AD, with both diseases eliciting an immune response against the expression of DAMPs [3, 13, 14].

Successful resolution of inflammation is characterized by the apoptosis of immune cells including neutrophils and macrophages and the clearance of any activated inflammatory cells [15]. In some studies, eosinophils are involved in resolving the inflammation, for example, through releasing interleukin-4 (IL-4) to induce muscle cell proliferation and regeneration, contributing to the resolution of muscle cell inflammation [16]. The body returns to the normal state of homeostasis without any long-term negative effects [17]. If the stimuli remain unresolved from acute inflammation, it can progress into chronic inflammation lasting months or even years [18]. The inflammatory cells continually infiltrate into the tissues which initially aim to clear existing cell debris and can start to cause damage to healthy residual tissues, resulting in the formation or exacerbation of neurodegenerative diseases [19].

Neuroimmune Responses

Neuroimmune responses arise from the interaction between the neural and the immune systems, protecting neural tissues against the invasion of pathogens [20, 21]. It consists of glial cells which include microglia, oligodendrocytes, and astrocytes, making up over 95% of all cells within the CNS [22]. In healthy conditions, glial cells take part in the homeostasis of various physiological activities within the brain [20], such as the regeneration of peripheral nerves [23] and CNS development by providing nutritional and structural support [24]. Astrocytes are responsible for regulating blood flow, clearing any excess neurotransmitters, and facilitating synapse formation [25, 26]; microglia serve as immunosensors of the stress response, monitoring the internal environment within the brain [27]; oligodendrocytes serve to myelinate axons of the CNS, speeding up the transmission of synaptic signals [28].

In pathological states, glial cells act as the first line of defense, mitigating the detrimental effects of disease by initiating an inflammatory response [20]. Microglia are specialized macrophages within the brain parenchyma that serve as the innate immune cells of the CNS [29, 30]. Like the peripheral immune system, they are activated in response to sterile (e.g., trauma) or infectious stimuli (e.g., bacteria and viruses) [29]. This activation leads to the production of proinflammatory immune factors within the brain (also known as neuroimmune factors), including chemokines, DAMPs, reactive oxygen species (ROS), reactive nitrogen species (RNS), and cytokines [19, 31]. These neuroimmune factors trigger a cascade of downstream reactions for an acute inflammatory response, known as neuroinflammation [32]. Chronic elevated levels of neuroimmune factors can increase the permeability of the blood-brain barrier (BBB), exacerbating neuroinflammation [33]. Neuroimmune factors such as interleukin-6 (IL-6) and interferon-gamma (IFN-γ) have been found to be associated with cognitive impairment and contribute to the development of AD (Table 1) [34].

Table 1. Key neuroimmune factors and associated immunological outcomes leading to neuroinflammation

Neuroimmune factor	Immunological outcomes	Reference
Interleukin 6 (IL-6)	• ↑Microglial proliferation • Release microglia-derived proinflammatory molecules and acute-phase protein • Lymphocyte differentiation	[35, 36]
Tumor necrosis factor-α (TNF-α)	• Microglial activation + phagocytosis of neurons → neuronal loss	[37]
Interferon-γ (IFN-γ)	• ↑Activation and proliferation of microglia • Upregulate activation markers • Stimulate β-secretase expression in human astrocytes: might enhance processing of amyloid-β (Aβ) • Induce polarization toward T helper (Th) 1 phenotype	[38, 39]
Transforming growth factor-beta (TGF-β)	• Enhance or inhibit astrogliosis depends on the context: the main source of the complement system proteins	[40]
Interleukin 1 alpha and beta (IL-1 α and β)	• Rapid proinflammatory response in astrocytes → ↑adhesion molecules, chemokines, cytokines, matrix metalloproteinases • Induce astrocytic expression of angiogenic factors: contribute to the dysfunction of BBB	[41]
High-mobility group box 1 (HMGB1)	• ↑Release of inflammatory factors such as TNF-α, IL-1β, and IL-6 • Can cause HMGB1-mediated neuroinflammatory response: bind to TLR4 and receptor for advanced glycation end products (RAGE)	[42]

Upon successful clearance of the etiological stimuli under favorable conditions, resolution of neuroinflammation takes place involving CNS remodeling and neural repair, followed by neurogenesis, angiogenesis, oligodendrogenesis, and remyelination [43]. However, unresolved inflammation within the brain can lead to the chronic activation of microglia, resulting in sustained upregulation of cytokines and ROS accumulation [43]. Activated microglia can also increase the calcium uptake into mitochondria, increasing the instability of mitochondria [44]. Ultimately, high levels of ROS and dysfunctional mitochondria can cause cumulative neuronal damage, contributing to the development of neurodegenerative diseases (Fig. 1) [45–47].

Gut-Brain Axis and Sterile Inflammation

Gut Microbiota and the Gut-Brain Axis

Gut microbiota represents the collection of bacteria, yeasts, archaea, and viruses that reside within the gastrointestinal tract, constituting around 10^{13}–10^{14} cells and forming a symbiotic relationship with the host cells [48–50]. There are six major phyla that dominate the gut microbial community, which are Actinobacteria, Bacteroidetes, Firmicutes, Fusbacteria, Verrucomicrobia, and Proteobacteria [51, 52]. Within the six phyla, Bacteroidetes and Firmicutes comprise over 90% of the total gut microbial population [51]. Although gut microbiota composition and diversity can be influenced by genes, it is predominantly determined by environmental factors, such as lifestyle (diet and exposure to environmental microbes) and modes of delivery [53, 54].

The gut and brain have been shown to communicate bidirectionally, forming the gut-brain axis [55]. Anatomically, this relationship is illustrated by the crosstalk occurring within the autonomic nervous system (Table 2) [56]. The extrinsic innervation of the gastrointestinal tract is provided by neurons that originate from the spinal cord and brainstem (Fig. 2) [57]. The vagus nerve plays a key role in modulating intestinal inflammation and gut homeostasis [58]. It can be activated by the gut microbiota directly and indirectly via short-chain fatty acids (SCFAs) released by the gut microbiota [59]. The intrinsic innervation of the gastrointestinal tract originates from the intestine, forming an enteric nervous system known as the myenteric and submucosal plexus across all the intestinal walls (Fig. 2) [57]. Communication can be done by the direct exchange of information through neurons, known as the neural pathway. In addition, components within both intrinsic and extrinsic nervous systems within the gut can form connections with the immune cells, regulating intestinal immunity [60].

Gut microbiota also facilitates communication with the brain via other pathways including humoral and immune

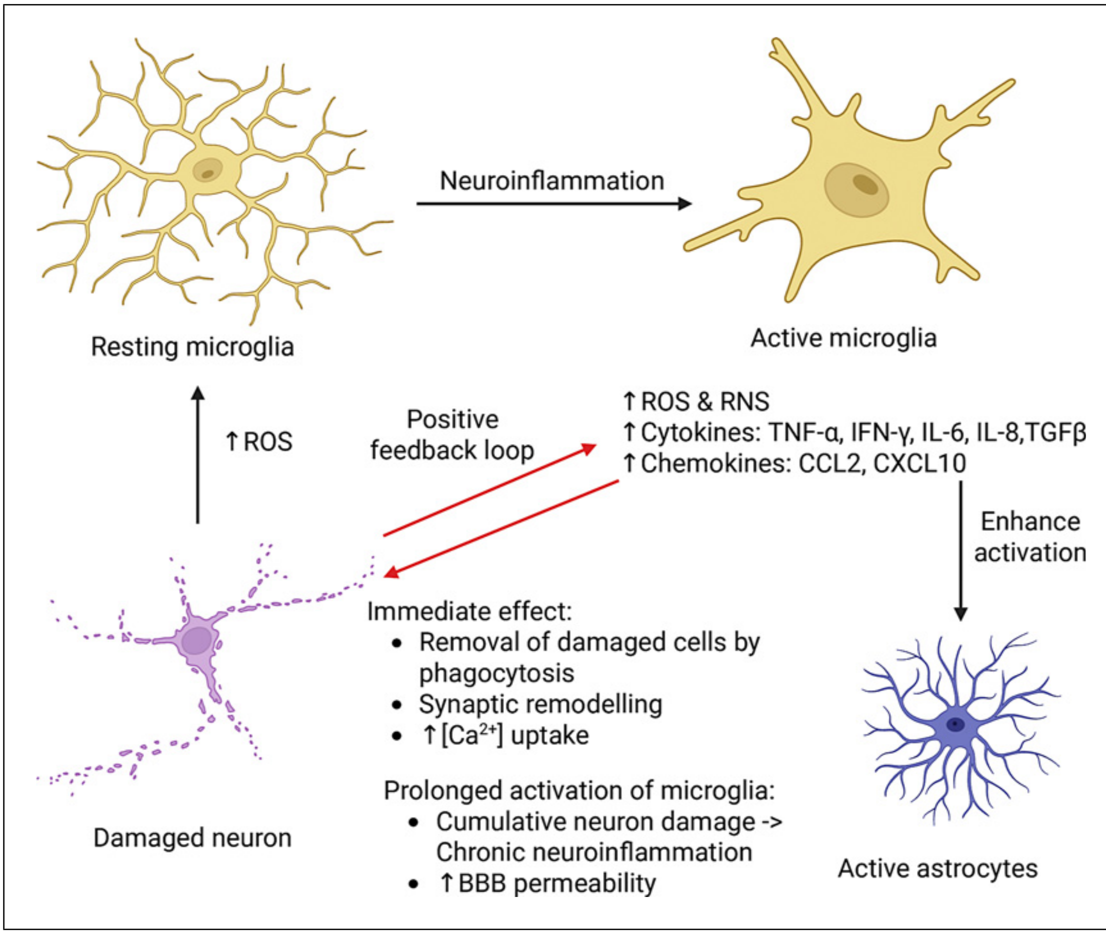

Fig. 1. Activation of microglia and neuroinflammation following neuronal damage. Neuronal injury leads to increased reactive oxygen species (ROS), activating resting microglia. Activated microglia further increases the level of ROS and reactive nitrogen species (RNS) and upregulates pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), interleukin-6 (IL-6), and transforming growth factor beta (TGF-β). The level of proinflammatory chemokines also increases, for example, chemokine ligand 2 (CCL2) and C-X-C motif chemokine ligand 10 (CXCL10). This is followed by the removal of damaged cells by phagocytosis and synaptic remodeling, aiming to restore the intracellular environment into a homeostatic state. There is also an increase in the uptake of Ca^{2+} ions by damaged neurons. Activated microglia can also further activate astrocytes. In the long-run, prolonged activation of microglia can lead to cumulative neuron damage, causing chronic neuroinflammation, with the increase of blood-brain barrier (BBB) permeability.

pathways [55]. All the pathways within the gut-brain axis are interrelated to facilitate effective communication between two organs to regulate various aspects of health, such as dietary components' metabolism, the integrity of the intestinal mucosal barrier, and intestinal homeostasis [65].

Microbial Imbalance, Sterile Inflammation, and Neurodegenerative Diseases

Microbial imbalance, in another word, "dysbiosis," refers to any disruption in the microbial population, causing a change in the stability and diversity of the microbial system within the internal environment [66]. The gut microbiome can be measured in terms of abundance and diversity [67]. In healthy individuals, a 16 s rRNA gene amplicon analysis from fecal microbiota demonstrated that the phyla Firmicutes and Bacteriodota have higher relative abundances than the phyla Proteobacteria, Actinobacteria, Fusobacteria, and Verrucomicrobia [68].

Neurodegenerative diseases are closely associated with microbial imbalance because of the gut-brain axis [69]. Patients with AD were found to have an increase in the abundance of proinflammatory bacteria such as *Shigella* and a fall in the abundance of anti-inflammatory bacteria such as *Eubacterium rectale* [70]. Similar results

Table 2. Overview of the origin of different gastrointestinal tract divisions and their implications on the gut-brain axis

Division	Origin	Gut-brain axis implication	Reference
Vagus nerve	Cranial parasympathetic nucleus	• Associated with depression and cognitive impairment • Maintain intestinal homeostasis	[61, 62]
Sympathetic nervous system	Preganglionic fibers: interomediolateral (IML) column of the spinal cord; postganglionic fibers: sympathetic chain/ganglia	• ↑Sympathetic activity can cause dysbiosis: result in imbalanced gut short-chain fatty acids (SCFAs) and plasma LPS level • Change in the level of metabolites produced by gut microbiota can affect bone marrow activity which can exacerbate central and peripheral inflammation	[63]
Enteric nervous system	Vagal neural crest cells, sacral neural crest cells (partial)	• Associated with neurodegenerative diseases • First site of α-synuclein aggregations which spreads to the brain via the enteric nervous system-vagus pathway	[64]

were also found in patients with PD [71]. As there is an increase in the population of pro-inflammatory bacteria, it promotes the intestine into a pro-inflammatory state, which is often associated with an increase in the permeability of the intestinal mucosal barrier [72]. Subsequently, the proinflammatory bacteria can produce detrimental metabolites or inflammatory factors such as IL-6 and tumor necrosis factor-alpha (TNF-α) that can diffuse across the mucosal barrier, causing sterile systemic inflammation [73]. Ultimately, the microbial metabolites can enter the brain through the pathways mentioned in section 2.1 along the gut-brain axis [72–74].

Chronic gut inflammation is capable of inducing neuroinflammation by inducing systemic inflammation through the upregulation of inflammation-promoting molecules [51, 75]. Recent studies also demonstrate the significant role of peripheral inflammation on brain functions, contributing to the pathogenesis of various neurodegenerative diseases [75–78].

Microbial Imbalance and Sterile Inflammation

Inflammasome Signaling

Inflammasomes are a group of cytosolic multiprotein complexes that can trigger the inflammatory pathway and cause cell death by activating pro-inflammatory caspase-1 [79]. They consist of a specific sensor protein (pattern-recognition receptors) that are activated in response to respective stimuli [80], an adapter protein that facilitates the assembly of inflammasome components, and an effector caspase such as pro-caspase 1, which activates pro-inflammatory cytokines [81]. The NOD-like receptor family pyrin domain-containing 3 (NLRP3) is a common example of pattern-recognition receptors, and its dysregulated activation is involved in the pathogenesis of neuroinflammation [79, 82]. NLRP3 has been found to be upregulated following the presence of a sterile stimulus such as a traumatic brain injury, triggering the inflammatory pathway [83]. In patients with AD, NLRP3 has been reported to exacerbate the progression and pathogenesis of AD by inducing neuron necrosis, apoptosis, and synaptic loss [84].

The gut microbiota can regulate peripheral inflammation via inflammasomes, indirectly modulating the CNS homeostasis via the gut-brain axis [85]. Different gut microbes and their derived molecules release pro-inflammatory cytokines via NLRP3 inflammasomes [86, 87]. For example, gram-negative bacteria such as *Escherichia coli* can bind to immunoglobulin G immune complexes within the intestine, stimulating bone marrow-derived macrophages to produce interleukin-18 (IL-18) and interleukin-1-beta (IL-1β) via NLRP3 [83]. This promotes peripheral inflammation [83]. In the case of microbial imbalance, the integrity of the intestinal mucosal barrier is compromised, allowing gut microbiota to release toxins from harmful gut microbes into the circulation which activates the NLRP3 inflammasome. [85]. This triggers the release of pro-inflammatory cytokines into the blood which stimulates the production of peripheral inflammasomes [85]. Once in the blood stream, these cytokines induce NLRP3-mediated neuroinflammation,

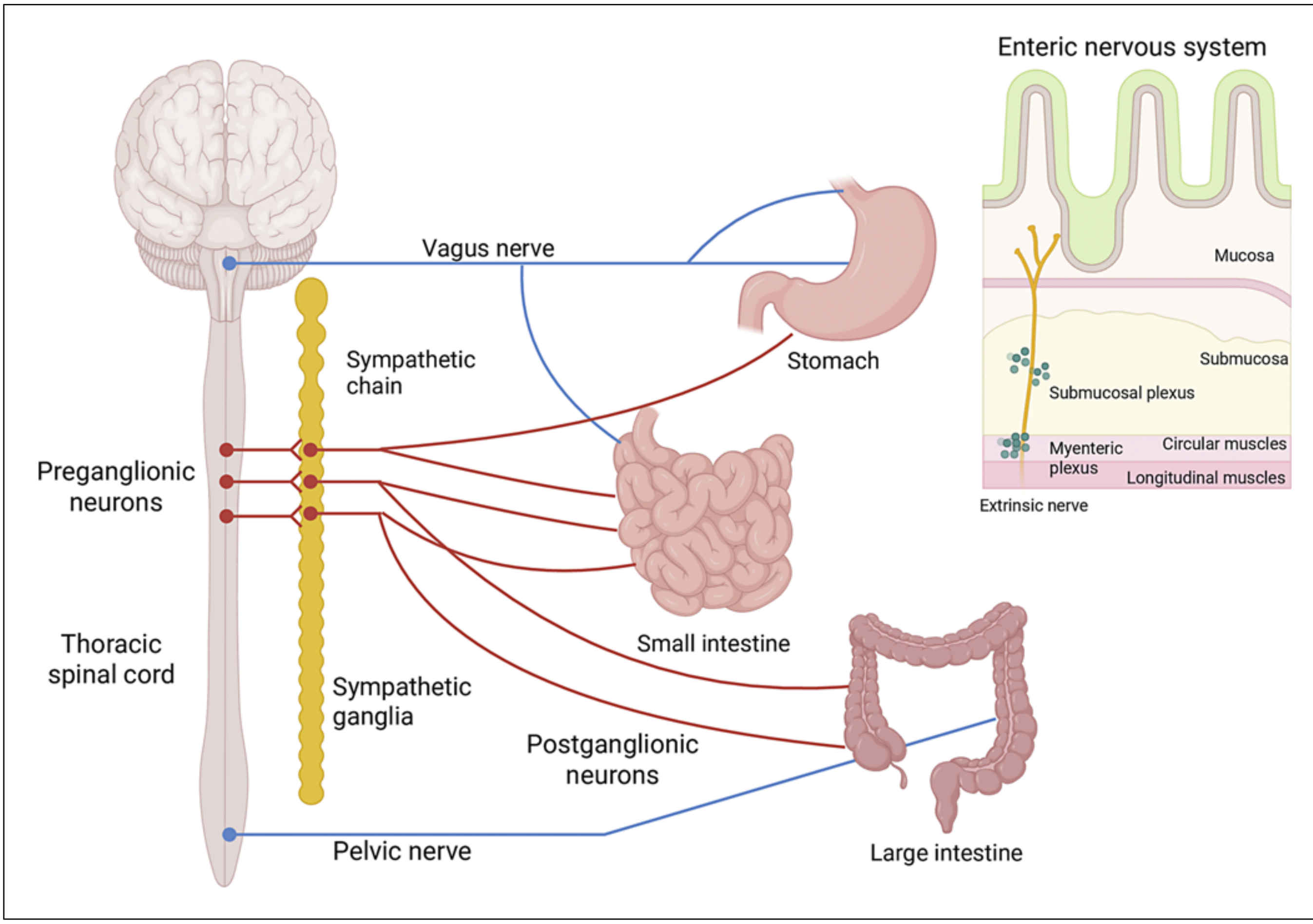

Fig. 2. Neuroanatomy of the gastrointestinal tract. The gastrointestinal tract is innervated by extrinsic and intrinsic nervous systems. Extrinsic innervation includes the parasympathetic vagus nerve supplying the part of the esophagus, the stomach, and the small intestine. The parasympathetic pelvic nerve supplies the distal colon and rectum of the large intestine. The sympathetic chain arising from the thoracic spinal cord supplies the stomach, the small intestine, and the proximal large intestine. The intrinsic innervation includes the enteric nervous system, consisting of the myenteric plexus and the submucosal plexus. They control various functions of the intestine such as gut motility, which can function independently without input from the CNS.

activating microglia within the CNS [83]. This is further supported by the findings in patients with AD and PD, where the chronic systemic inflammation triggered by the activation of NLRP3 by gut microbes contributes to neuroinflammation [86, 88, 89].

Altered Permeability of the BBB by the SCFAs

The BBB is an important border that controls the entry and exit of substances into the CNS, contributing to CNS homeostasis by preventing the entry of unwanted substances, such as toxins and pathogens [90]. Increase in the permeability of the BBB can facilitate the entry of toxic molecules from gut microbiota like lipopolysaccharides (LPS) [91, 92]. Toxins entering the brain can activate pro-inflammatory cytokines such as TNF-α, promoting neuroinflammation [92, 93]. A recent study also confirmed that patients with PD also experience BBB degradation via the activation of tyrosine kinase discoid in domain receptor 1 (DDR1) [94].

Gut microbiota transforms dietary fibers into diverse types of metabolites such as SCFAs (e.g., acetate, propionate, and butyrate) and amino acid derivatives [95, 96]. Gut microbiota and their metabolites are known to be important modulators on the permeability of the intestinal mucosal barrier of the gut and the BBB of the brain [97, 98]. This is achieved through regulating the expression of tight junction proteins such as occludin and claudins, which function as a barrier in endothelial tissues [99, 100]. It has been reported that the basal nontoxic level of SCFAs can cross the BBB and improve the integrity of BBB by upregulating the tight junction proteins [101]. In patients with PD, a lower relative abundance of SCFA-producing bacteria was observed along with an altered gut microbiota composition [102–104]. Similar results were also found among patients with AD [105, 106].

Oxidative Stress and Inflammatory Responses

ROS are highly reactive particles produced in mitochondria as a by-product of cellular respiration [107]. Metabolites and antioxidant enzymes produced by the gut microbiota can regulate mitochondrial activities via various signaling pathways, altering the ROS levels [107, 108]. Formylated peptides are commensal gut metabolites that can bind to G protein-coupled receptors on neutrophils and macrophages [108]). This produces superoxide as a ROS by NADPH oxidase 1 (NOX-1) [109]. Specific genera of gut microbiota, for example, *Bifidobacterium*, can form nitric oxides leading to RNS, making the intestinal epithelia susceptible to the damage of ROS [108]. Within the normal levels, ROS and RNS play a key role in various physiological processes, such as facilitating intracellular and extracellular messengers and modifying proteins (e.g., JUN protein) [110].

When the redox homeostasis fails, an imbalance of ROS takes place which can execute oxidative stress [111, 112]. This can destroy organic molecules such as proteins, lipids, and DNA, causing tissue and cell death [113]. An alteration in composition and diversity of gut microbiota can favor the production of detrimental metabolites, exerting higher oxidative stress onto the environment for an inflammatory response [114]. This is followed by the infiltration of macrophages and neutrophils into the gut which further produce ROS, attracting more immune cells toward the injured site, exerting more oxidative stress and forming a positive feedback loop for the inflammatory response within the gut (Fig. 3) [114].

Considering that the brain consumes a large amount of oxygen and is rich in lipids, it is highly vulnerable to oxidative stress [115, 116]. Translocation of bacterial materials from the gut to the brain can alter the oxidative stress levels within the brain [117]. LPS is known to stimulate oxidative stress by inhibiting the activity of superoxide dismutase and reducing the levels of glutathione [118]. It also increases lipid peroxidation, which is closely associated with neurodegenerative diseases [118]. It has been reported that LPS from intestinal gram-negative bacteria can activate NF-κB signaling via Toll-like receptor 4 (TLR4) in the hippocampal neurons of rat models, causing LPS-induced inflammation within the brain [35, 118]. A recent study demonstrated that LPS within PD-associated brain regions, such as the striatum, play a significant role in activating the microglia for a neuroimmune response by activating the nuclear factor-kappa B (NF-κB) signaling pathway [36]. This provides primary evidence of the pathophysiological role of ROS exerted by gut microbiota on neuroinflammation.

Would Gut Microbiota Be Novel Therapeutic Targets to Modulate Neuroinflammation?

With emerging evidence demonstrating the importance of gut microbiota in modulating the gut-brain axis, it is now known that maintaining a balanced and stable gut microbiota population is crucial for health. Knowing the relationship between gut microbiota and inflammation, scientists have begun to conduct experiments exploring the potential roles of administering gut microbiota in health. Probiotics refer to live microorganisms that are thought to be beneficial to the host's health state when sufficient levels are being administered [37], for example, *Lactobacillus* and *Bifidobacterium* species, that are thought to promote gut health [38, 39]. Growing research studies suggest that probiotics can activate anti-inflammatory pathways [40]. This can be achieved through modulating the balance between regulatory T (T_{reg}) cells and T helper (T_h) cells, thereby inhibiting proinflammatory cytokines like IL-6 and producing anti-inflammatory cytokines such as IL-4 [40]. *Lactobacillus* and *Bifidobacterium* are excellent probiotics which can be found in various food sources such as kimchi and yogurt [40, 41]. Certain strains of *Bifidobacterium longum* have been found to be effective in upregulating the transcription factor forkhead box P3 (FOXP3+) T_{reg} cells within the intestine, which are responsible for secreting the anti-inflammatory cytokine IL-10 [41]. Furthermore, *Lactobacillus acidophilius*, *Bifidobacterium bifidum* and *B. longum NK46* can prevent Aβ-induced cognitive dysfunction and dampen inflammation synergistically, observed within the hippocampus of mice models with AD [42, 61].

The administration of probiotics also regulates intestinal homeostasis by increasing the number of beneficial commensal bacteria [62]. The colonization of beneficial commensal bacteria causes competition exclusion, preventing the pathogenic bacteria to grow within the gut, promoting a balance within the gut

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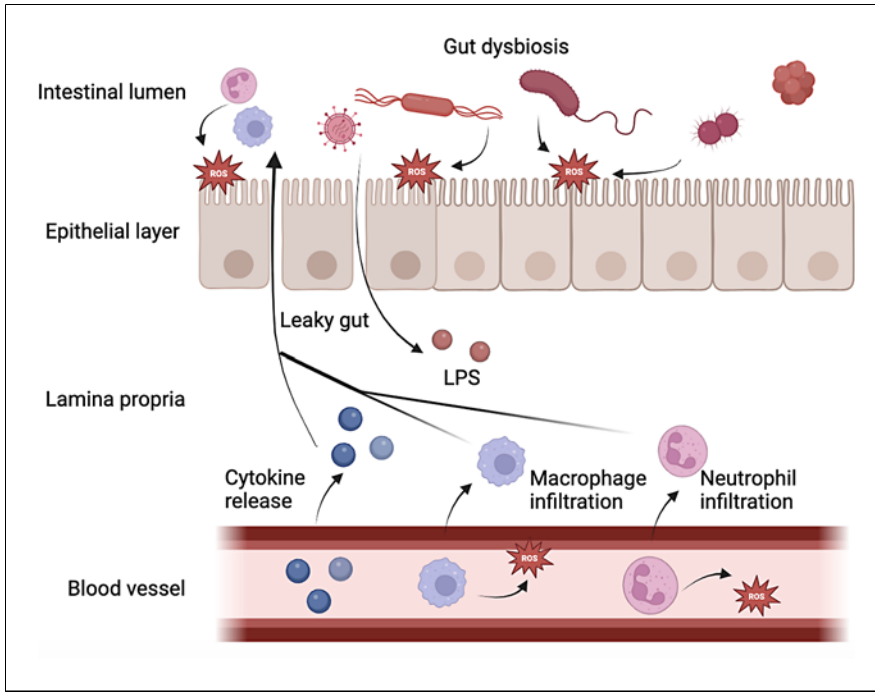

Fig. 3. Systemic inflammation resulting from microbial imbalance. Microbial imbalance in the intestinal lumen exerts reactive oxygen species (ROS) which poses oxidative stress onto the epithelial layer of the intestine. It also increases intestinal permeability ("leaky gut"), enabling lipopolysaccharides (LPS) produced by certain populations of gut microbiota to escape into lamina propria and eventually into systemic circulation. In response to ROS, proinflammatory cytokines are released from blood vessels into the intestinal lumen. This is also accompanied by the infiltration of macrophages and neutrophils from the blood vessels, which release ROS into the systemic circulation, increasing oxidative stress.

microbiota population [63]. For example, a significant reduction in *Vibrio cholerae* (pathogenic bacteria) is achieved through administering probiotics in an infant mice model [63, 64]. This then promotes the growth of *Lactobacillus* which stimulates lactic acid production, contributing to intestinal health [64].

Higher levels of beneficial bacteria within the gut also allow higher levels of their beneficial metabolites to be secreted, which have positive effects on gut health. For example, improving the relative abundance of *B. longum* can increase the rate of production of butyrate [119]. It is a SCFA that helps lower ROS by influencing mitochondrial activity [119]. Butyrate has also been found to be effective in dampening an inflammatory response among animal models with AD [120]. Moreover, SCFAs could regulate circadian rhythms across various tissues in wild-type mice [121]; and potentially help alleviate the circadian disruption induced by systemic inflammation and neuroinflammation [122].

Furthermore, having a balanced gut microbiota population has been shown to be able to enhance the integrity of the intestinal barrier and the BBB [123]. This is supported by a study on mice models which demonstrated improved levels of expression in claudin-5, occludin, and ZO-1 after administering a mixture of *Lactobacillus* compared to controls [124]. Based on some epidemiological and experimental studies, it has been reported that the butyrate-producing genera of *Firmicutes* such as *Anaerostipes* and *Faecalibacterium* are the next-generation probiotics or even live biotherapeutic products [125–127].

In the past decades, there have been clinical trials and research studies on the potential efficacy of probiotics in modulating the progression of neurodegenerative diseases [37, 72, 86, 128, 129], most of which demonstrated positive results in alleviating the symptoms, demonstrating the potential therapeutic values of probiotics as an adjunctive therapy for neurodegenerative diseases [86, 87, 104, 130, 131]. However, there is still a large area of unknown in this field which requires further research in confirming its therapeutic utility, for example, the exact mechanisms of actions of gut microbiota. Although a relationship is delineated between the gut microbiota and the neurodegenerative disorders, it remains unclear about their exact roles in modulating neuroinflammation. Furthermore, the complex underlying mechanism for the development of neurodegenerative diseases has not been fully elucidated, making them challenging to reach a cure nowadays.

Conclusion

There is an increasing interest in investigating the roles of gut microbiota on mediating and modulating inflammation over the past years, as well as their effects on distant organs of the body. The gut-brain axis has been identified with promising evidence with gut microbiota as a modulating agent in neuroinflammation; however, information on the pathophysiological role of gut microbiota in the development of neurodegenerative diseases is still limited. Current published studies focus on epidemiological findings identifying the associations between gut microbiota and neuroinflammation. The effectiveness of using gut microbiota as a novel therapeutic target in neurodegenerative diseases is still unclear due to the limited number of clinical studies. It is important for one to take note that the use of dosage, strains of probiotics, way of administration, and time interval are factors that can affect effectiveness. The feasibility of making probiotics part of the routine treatment for neurodegenerative diseases is still yet to be discovered. Based on current understanding, three successive pathways in inducing neuroinflammation by the gut microbiota have been identified, including inflammasome signaling, BBB integrity alteration, and oxidative stress. Chronic systemic inflammation is often involved, suggesting the indirect modulatory role of gut microbiota on the brain.

Acknowledgment

All figures were generated in BioRender (biorender.com).

Conflict of Interest Statement

Prof. Raymond Chuen-Chung Chang was a member of the journal's editorial board at the time of submission. The remaining authors have no conflicts of interest to declare.

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Author Contributions

P.-Z.L.: writing – original draft and conceptualization. K.-H.W. and Y.-S.-H.: writing – review and editing. W.-Y.C. and R.C.-C.C.: conceptualization, supervision, and writing – review and editing.

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