The Gut–Microbiota–Brain Axis in Neurodegenerative Disorders: Molecular Mechanisms, Immune Interactions, and Therapeutic Opportunities.

Abstract

Neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS) are an escalating global health concern, having a progressive neuronal loss and the inadequate curative treatments. In recent years scientists have discovered a pathway linking gut health to neurodegeneration through the critical gut–microbiota–brain axis (GMBA) pathway. This review examines how gut microbiota dysbiosis highlighted by reduced microbial diversity due to depletion of beneficial bacteria and overgrowth of pathogenic species favours disease progression. Dysbiosis disrupts intestinal barrier integrity, leading to increased permeability and systemic translocation of microbial products such as lipopolysaccharides (LPS), which triggers pro-inflammatory cytokine release and neuroinflammation. These inflammatory processes impair the blood-brain barrier, activate microglia, and promote neuronal damage. Moreover, a decrease in the production of the short-chain fatty acids (SCFAs), especially butyrate, compromises immune regulation and neuroprotection whereas altered microbial metabolism affects neurotransmitter synthesis and signaling. Various factors such as diet, aging, medication use, and lifestyle significantly impact gut microbial composition. The review further explores therapeutic strategies, including dietary inventions, probiotics, prebiotics, fecal microbiota transplantation and emerging approaches like psychobiotics, emphasizing their potential to restore microbial balance and mitigate neurodegeneration.

Introduction

Neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS) are a growing global health concern, with an estimate of 152 million people being affected by 2050 (Gadhave and Sugandhi)1. This review will explore the connection between imbalanced gut microbiota and neurodegenerative diseases. Despite extensive research, these disorders remain incurable, due to the progressive

loss of structure and function of neurons in the brain. Notably, patients detected with neurodegenerative diseases commonly exhibit a trend in poor gut microbiota, as it is associated with a decline in beneficial microbes causing an increase in opportunistic pathogens(V)2. These diseases are significantly more prevalent in the elderly population due to age-related factors such as reduced intestinal motility, decreased digestive enzymes and weakening of the gut lining. This contributes to increased intestinal permeability (leaky gut). Additionally, excessive intake of medications, erodes good bacteria resulting in overgrowth of pathogenic species, highlighting a strong association between neurodegenerative diseases and gut microbiota imbalance, suggesting new therapeutic avenues focused on restoring gut health. Gut microbiota is a complex community of ~100 trillion microbes residing along the inner surface of the gastrointestinal tract present in the intestine. A healthy gut microbiota plays a crucial role in host gene expression, immune system development, pathogen colonization resistance, nutrient absorption, vitamin and neurotransmitter production and other physiological functions (Sender and Fuchs)3. Conversely, a gut dysbiosis—an imbalance in microbial composition— influences the release of bacterial products such as a Lipopolysaccharide (LPS) into the bloodstream, this triggers a systemic immune response and the secretion of pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6) (Hill and Round)4. These inflammatory signals cause disruption of the blood-brain barrier, neuroinflammation, microglial activation, and subsequent neuronal damage by accessing the central nervous system via the gut–brain axis—a bidirectional communication network linking the central nervous system (CNS) with the gastrointestinal tract and it happens via neural (e.g. vagus nerve), endocrine (e.g., HPA axis), immune, and metabolic pathways (Sender and Fucas)5. This review explores the therapeutic potential of maintaining a healthy gut microbiota in mitigating the progression of neurodegenerative diseases. To better understand this relationship, it is essential to examine the composition and functional roles of the gut microbiota in maintaining physiological homeostasis.

Composition and Functional Metabolism of the Gut Microbiota

The gut microbiota refers to the diverse community of microorganisms inhabiting the human gastrointestinal tract, primarily composed of bacteria from the phyla Firmicutes, Bacteroidetes,

Verrucombria, Actinobacteria, and Proteobacteria, along with fungi, viruses, and archaea (Romero et al)6. These microbes perform essential functions such as digestion of complex polysaccharides, synthesis of K and B vitamins, regulation of immune responses and protection against pathogenic invasion (Health)7. However, the primary function of the microbes is fermenting undigested dietary components like the fiber, protein, lipid and host molecules and producing the metabolites particularly the short-chain fatty acids (SCFAs) such as the butyrate, acetate, and propionate. These compounds reinforce intestinal barrier function, exert anti-inflammatory effects, regulating glucose and lipid metabolism, and influencing host immune responses. The SCFAs, particularly butyrate, serve as a major energy source for colonocytes and contribute approximately 10% of the body's daily energy requirements (Araújo)8. Propionate is mainly involved in producing glucose in the liver and small intestine and acetate is important for energy production and synthesis of lipids. The formation of SCFAs is highly influenced by a diet inculcating various soluble and insoluble dietary fibers (they are the non-digestible polysaccharides (NDPs) of cell walls of plants). Firstly, the soluble fibre sources food containing components Galactomannan, Pectin, Psyllium husk and galacto-oligosaccharides (GOS). Wheat dextrin and resistant starch is present in food such as apples, citrus fruits, carrots, beans, and, green raw potatoes, lettuce, oats, guar bean, algae, bacteria and mushrooms. Including the soluble prebiotic fibers inulin majorly present in garlic, onions. Along with the whole grains consisted of complex polysaccharides like beta-glucans and arabinoxylans and also legumes such as lentils and chickpeas. The existence of Fructo-oligosaccharides (naturally occurring, non-digestible carbohydrates that function as prebiotics) found in bananas (Chin et al)9. While the insoluble fibre present in cellulose, cellulose, hemicellulose, chitin, chitosan, lignin, suberin, and cutin does not contribute directly to SCFAs production but greatly affect the growth of bacteria producing SCFAs (Sankarganesh et al)10. Given the critical functions of gut microbiota, its interaction with the intestinal barrier is essential in regulating host health and preventing systemic dysfunction.

Structure of the Intestinal Barrier in Maintaining Systemic and Neural Integrity

The intestinal barrier is a multilayered defense system located along the inner wall of the gastrointestinal tract primarily in the small and large intestine. It forms the critical interface between the gut lumen which contains the digested food particles and the microorganisms, and the internal environment of the body. The intestinal barrier regulates interactions between the gut microbiota and the host, helping maintain immune balance while preventing the invasion of the pathogens, toxins and microbial components from entering the systemic circulation. By regulating permeability and immune responses, the intestinal barrier maintains homeostasis, as it preserves the stability of the gut microenvironment (Gou et al)11. This function is achieved through several coordinated layers within the intestinal barrier. The first layer is the mucus layer secreted by goblet cells, which forms a gel-like protective coating over the intestinal surface which is organised in two layers: a more loose, outer layer where most of the intestinal bacteria reside, and a dense, inner layer that does not contain bacteria. This acts as a physical barrier, separating intestinal lumen from the underlying tissue as the mucus traps the microbes. The outer layer of the mucus acts as a nutrient source to the communal bacteria so it stabilizes the balance of intestinal flora (Sergi)12. Beneath the mucus lies a single layer of intestinal epithelial cells, including enterocytes, goblet cells, paneth cells, and enteroendocrine cells. These cells are tightly connected by tight junction proteins, a selective transport barrier which regulates intestinal permeability as it prevents toxic bacterial products such as lipopolysaccharides (LPS) from entering the bloodstream and causing systemic inflammation (Dmytriv et al)13. Specialized cells such as the paneth cells produce antimicrobial peptides (AMPs) that kill harmful bacteria allowing the beneficial commensal microbes to live in the mucus layer. Below the epithelial layer lies the gut-associated lymphoid tissue (GALT), which contains immune cells such as macrophages & dendritic cells. In this layer the barrier cooperates with the immune system and releases Secretory Immunoglobulin A (sIgA) a primary antibody which is coated on the beneficial bacteria helping to reduce inflammation and thus the microbial population can be managed efficiently without eradicating them (Tommaso et al)14. This layer also regulates the immunogenicity of intestinal antigens is a type of innate immune system that can induce the differentiation of the T cells and activates the adaptive immune system (ogino et al)15, also supports the anti-inflammatory properties of dendritic cells, contributing to immune homeostasis

(Fu et al)16. Therefore, the intestinal barrier plays an essential role in protecting the central nervous system (CNS) with the barrier preventing the microbial toxins from entering the circulation, reducing the systemic inflammation and regulates the immune response. Beyond its protective role, the intestinal barrier also facilitates communication between the gut and the brain, enabled by complex neurosignalling pathways.

Microbiota-Mediated Neurosignalling

Neurosignalling occurs via the bidirectional gut brain axis to convey sensory information such as nutrition detection and mechanical changes from gut enteroendocrine cells directly to the brain and motor control (brain-to-gut), regulating digestion and immune responses through the vagus nerve. Gut microbiota is essential for neurosignalling as it contributes to stimulating vagal afferent neurons, producing neurotransmitters and modulating signals sent from the gut to the brain (Kim et al)17. The microbes are also responsible for producing neuroactive compounds which are neurotransmitters and their precursors influence mood and cognition, such as serotonin, dopamine and gamma-aminobutyric acid (GABA). Serotonin is produced by Staphylococcus Clostridial species and it regulates intestinal motility. Dopamine is produced by Staphylococcus and it influences release of gastric juices, modulates the movement of the stomach, including peristalsis and gastric emptying. This impacts blood circulation in the stomach lining, playing a major role in nutrient delivery and maintaining tissue integrity. GABA is produced by Bifidobacterium, Bacteroides fragilis, Parabacteroides and Eubacterium and it is for the modulation of the synaptic transmission in the enteric nervous system simultaneously regulating intestinal motility and inflammatory responses (Chen et al)18. The gut microbiota is vital in neurosignalling, which is affected by various factors.

Determinants of Gut Microbiota Composition

The function and the composition of the gut microbiota is influenced by several factors like genetics, age, stress levels, lifestyle habitats (exercise), environmental factors, the mode of

birth, infant feeding method and the usage of medications, especially antibiotics, but mainly is diet (Wen and Duffy)19. Firstly the diet, a meal rich in fiber, plant based diets (such as the Mediterranean diet consisting of vegetables, fruits, olive oil, and whole grains) act as prebiotics, feeding beneficial bacteria like Bifidobacterium and Lactobacillus, having a healthy diversity promotes the control of inflammation and reduction of free radicals which cause illness, aging and supports the improvement of the metabolic health. Even probiotic food like yogurt, kefir and kimchi lead to an introduction of live beneficial microbes directly into the gut (Slavin)20. Whereas, processed food like diets high in refined sugars and saturated fats (Western diet) reduces microbial diversity (depletes protective bacteria like Akkermansia muciniphila) and encourages growth of Escherichia. coli, Salmonella, and Shigella which are the harmful species (Statovci et al)21. Food addictives: sweeteners and emulsifiers also negatively impact the microbiota. Sweeteners like saccharin sucralose and aspartame gain glucose intolerance by altering the gut's microbial community and the emulsifiers like carboxymethylcellulose (CMC) and polysorbate 80 (P80) trigger inflammation by reducing the mucus thickness and impairing the intestinal barrier of the gut (Gultekin et al)22. Secondly, medication eradicates the microbial diversity as antibiotics are the major destroyers that can kill both the beneficial and harmful bacteria (Ramirez)23 and other drugs like proton pump inhibitors, laxatives and certain antipsychotics alter the gut pH (Imhann et al)24. Even the mode of delivery of the child plays an essential role as vaginally born infants are exposed to their mother's vaginal and fecal bacteria which promotes the microbial diversity whereas C-section infants are in contact with the skin microbes thus reducing the microbial diversity (Zhang et al)25. The microbial diversity is nourished when the infant is breast fed as breast milk contains sugars called Human Milk Oligosaccharides (HMOs) that are specifically functioned to feed beneficial bacteria (Bifidobacteria) (Wickramasinghe)26. Lifestyle also influences microbial diversity, like exercising, stress and sleep. Regular exercise increases production of the beneficial short chain fatty acids (SCFAs) thus raises the microbial diversity (Varghese et al)27 whereas, stress alters the gut motility and hormone levels leading to an unbalanced microbial via the gut brain axis, changing the proportion of the main microbial phyla and causing the intestinal permeability to rise. Sleep deprivation is related to the decrease of Lactobacillus and Bifidobacterium and

promotes pro-inflammatory cytokines like IL-6 and TNF-α (Foster et al)28. Exposure to heavy metals and pesticides impacts an individual's microbial by increasing pro-inflammatory Proteobacteria and diminishing the beneficial SCFA-producers (Ma et al)29. These factors play a major role in the functionality of the gut–brain axis.

The Gut–Microbiota–Brain Axis

The Gut-Microbiota-Brain Axis (GMBA) is a bidirectional communication pathway connecting the gut, its microbiota and the central nervous system (CNS) and the enteric nervous system (ENS) via neural, endocrine and immune signals. This communication occurs through the release of the neurotransmitters, cytokines, microbial metabolites, and other signaling molecules. Neural signalling (vagus nerve), immune signalling, microbial metabolite signalling (SCFAs), endocrine signalling and tryptophan metabolism and neuroactive compounds are the 5 pathways through which communication occurs efficiently. Immune signaling in the gut brain axis relies on both direct pathways like the stimulating of immune cells into the brain and indirect pathways such as releasing of cytokines and microbial metabolites into the systemic circulation where the immune system translates signal from the gut microbiota into physiological and behavioral changes in the brain (O'Riordan et al)30. The pro inflammatory cytokines like Interleukin-6 (IL-6), Tumor necrosis factor-α (TNF-α) and Interleukin-1β (IL-1β) are released by the peripheral immune cells in the gut in response to the microbial stimuli which then crosses the blood brain barrier (BBB) by active transport or enter through regions like circumventricular organs aiming to influence neuronal activity and trigger neuroinflammation (Lucerne and Kiraly)31. Immune signalling is also modulated by the production of microbial metabolites, the metabolites are tryptophan and SCFAs. SCFAs like acetate and butyrate produced by the bacterial fermentation in the gut which crosses the BBB and contributes to the maturation and function of the microglia and gene expression in brain cells. Tryptophan is an amino acid that can be converted into serotonin, kynurenine metabolites and indole derivatives which impact neurotransmission, immune regulation and neuroinflammation. Indoles derivatives by gut bacteria (E. coli) activating Aryl

Hydrocarbon Receptors (AHR) on astrocytes and microglia for suppressing neurotoxic inflammation (Parker et al)32. Endocrine signalling is an interaction between the gut and the brain via the microbiota-gut-brain axis (MGA) that impacts stress levels, mood, sleep and by the release of essential hormones (cortisol, serotonin and melatonin) and neurotransmitters (Rusch et al)33. Cortisol, a stress hormone, which is regulated by the hypothalamic–pituitary–adrenal (HPA) axis. In cases of microbiome imbalance, this system becomes overactive, leading to elevated cortisol levels associated with anxiety and depression (Lu et al)34. Melatonin is a sleep hormone synthesized in the brain and gut as the gut microbes affect the production helping to regulate the body's circadian cycles and sleep-wake cycles (X et al)35. About 90-95% of the body's serotonin, a crucial neurotransmitter also the happiness hormone, is produced in the gut by enterochromaffin cells, a group of specialised cells which are accountable for mood, sleep, digestion, and appetite. The gut bacteria Lactobacillus and Bifidobacterium, nurture serotonin synthesis by raising the availability of its precursor or tryptophan (Wei et al)36. The production of the hormones in the gut supports emotional regulation and cognitive clarity by gut-derived serotonin and GABA and suppression of the stress hormones (Chadaram et al)37. One of the main outcomes of gut–brain axis signalling is its impact on microglial activity, which plays a crucial role in maintaining neural health.

Microglial Dynamics in Neuroinflammation

Microglia are tissue-resident macrophages that make up around 5–15% of total brain cells and have several well-defined functions in the central nervous system (Sender and Fucas)38. The microglia has three stages of development, early, pre- and adult. When the brain first develops the stages, early and pre-microglia play an important role in the synaptic remodeling and subsequent shaping of the neural circuitry and regulating the number of neurons through mechanisms of programmed cell death (PCD) (Pelvig and Pakkenberg)39. A few weeks after birth, microglia transits to the adult stage, constantly to maintain homeostatic conditions and release pro- and anti-inflammatory signalings to clear pathogens and repair tissue damages to restore brain health (Sierra and Encinas)40. However, in the presence of persistent pro-inflammatory signaling, microglia can become chronically overactivated and the etiologic factor

of neurodegenerative disease. Due to the dominance of pro-inflammatory responses over anti-inflammatory signaling, resulting in neuronal damage instead of preventing development of chronic inflammation and allowing microglia to maintain their neuroprotective and wound-healing properties (Haq and Schlachetzki)41. The coding and noncoding risk alleles of neurodegenerative and behavioral diseases highly influence the genes highly or preferentially expressed in microglia. However, disruptions in gut microbial balance can alter microglial function, highlighting the significance of gut dysbiosis.

Gut Microbiota Dysbiosis as a Driver of Neurodegenerative Pathology

Gut dysbiosis is the imbalance in the composition, diversity and function of the gut microbiota characterised by loss of beneficial bacteria, overgrowth of pathogenic microbes and reduced microbial diversity. The maintained homeostasis in the gut is disrupted as the intestinal barrier, a protective lining impairs, the immune regulation is altered and an increase in the intestinal permeability where the barrier becomes porous (DeGruttola et al)42. The microbial composition of the necessary bacteria such as Lactobacillus, Bifidobacterium, and Faecalibacterium prausnitzii depletes resulting in the decrease of the SCFA production especially butyrate, necessary energy source for the gut cells. Furthermore, there is a reduced induction of the calming immune signals as the anti-inflammatory effects are weakened and loss of barrier support leading to loss of molecules which reinforce cell to cell junctions. On the other hand, there is a bloom of harmful bacteria, an expansion of the Proteobacteria including the pathogenic Escherichia coli and certain Clostridium species. They are responsible for toxic production as harmful metabolic byproducts are released, they also actively feed on the protective mucus layer causing degradation of mucus in the gut promoting inflammation (Martín et al)43. As the dysbiosis exacerbates there is greater failure in the gut's defensive secretions as less mucus, SCFAs, and antimicrobial peptides (AIMPs) are produced, along with a decrease in the secretory IgA (sIgA) thus less neutralising of pathogens. Simultaneously, the levels of the Lipopolysaccharides (LPS) and bacterial toxins escalate, weakening the epithelial cells and disrupt tight junctions, facilitating massive leakage (Shen et al)44. An alteration of the

microbial metabolites like the SCFAs lead to ineffective monitoring on the immune cells, loss of barrier integrity and deprivation of the direct signalling to the nervous system. Elevated levels of the LPS ammonia and the hydrogen sulfide hinder the host environment by driving systemic inflammation, oxidative stress and ultimately neuroinflammation (Tan et al)45. The disruption of the barrier allows microbial components like the LPS(endotoxin) to translocate into the bloodstream then the LPS bind to the Toll-like receptors (TLRs) on plasma membrane surface of the innate immune cell, triggering the cytokine production by the signaling pathways like NF-κB (Perros)46. Activation of the NF-κB leads to large figures of pro-inflammatory cytokines, TNF-α, IL-6, and IL-1β accentuating gut inflammation before entering the systemic circulation and thus amplifying the immune response throughout the body; this is the chronic low-grade systemic inflammation (Zhang et al)47. Reduction in the SCFAs also decreases the regulatory T cells (Tregs)48 without which the body loses its immune tolerance resulting in the immune system to become permanently overactive and dysregulated (Liu et al)49. Dysbiosis generates a self perpetuating loop of Dysbiosis → Inflammation → Barrier Damage → More Leakage → More Inflammation having each step strengthen the next, worsening the condition. The inflammatory mediators establish a body-wide inflammatory state as they spread via the blood to the liver, metabolic tissues, general immune system and the brain (Li et al). The inflammation reaches the brain through 3 primary pathways, the blood circulation as the cytokines and LPS travel systemically, the vagus nerve as direct neural signaling from the gut to the brainstream and the immune signalling where the enlisting of peripheral immune cells to the brain lead to microglial activation, BBB disruption and release of inflammatory mediators within the CNS (O'Riordan et al)50. Worsening of the GBA ultimately drives the neurodegeneration, the list of the neurodegenerative diseases:

Alzheimer's Disease (AD): Linked to increased Escherichia/Shigella and H.pylori, which promotes amyloid-beta accumulation and neuroinflammation.

Parkinson's Disease (PD): Associated with nurturing of Enterobacteriaceae Desulfovibrio, which are linked to □-synuclein aggregation and motor deficits (Wu et al)51.

Multiple Sclerosis (MS): Characterized by dysregulated T-cell responses and a specific microbial signature involving Akkermansia and Acinetobacter (Cekanaviciute et al)52.

However, it remains unclear whether gut dysbiosis is a primary cause of neurodegenerative diseases or a consequence of disease progression, highlighting a major limitation in current knowledge.

Therapeutic Strategies Targeting the Gut–Microbiota–Brain Axis

Involvement of therapeutic implication will help achieve a healthy gut and lower the chances of neurodegenerative diseases. Firstly, diet is the most common factor shaping gut microbiota and gut–brain axis function. A beneficial diet would be mediterranean, DASH and mind diet which is rich in fiber, polyphenols and omega-3 fatty acids and promote butyrate-producing bacteria thus a rise in SCFAs exhibiting a decrease in inflammation, amyloid-beta accumulation and cognitive decline. Even the ketogenic diet is effective as it includes ketosis which is an alternative brain energy source that helps in modulating microbiota, reduces inflammation and alters microglial activation. Whereas the western diet is a threat to the gut as it is high in fat, refined carbs and low fiber leading to dysbiosis, increased harmful bacteria and thus inflammation. Secondly, microbiota based therapies consist of Probiotics, Prebiotics, Synbiotics, and Postbiotics (PPSP). Probiotics are a group of good bacteria like Lactobacillus, Bifidobacterium that help to improve gut barrier, reduce inflammation and increase SCFAs. Prebiotics are a group of specialised plant fibers, primarily non digestible carbohydrates like insulin and fiber on which beneficial medicines feed and it also enhances the SCFAs production. Postbiotics are the non living microbial metabolites which affect the anti-inflammatory and immunomodulatory but not all diseases respond like there is no effect in Huntington's disease. Thirdly, Fecal microbiota transplantation (FMT) where a healthy donor transfers its microbiota to improve the cognition avoiding AD and it also improves motor function avoiding PD along with that there is protection of the dopamine neurons, however, there is an infection risk and common gastrointestinal symptoms. Fourthly, emerging and alternative therapies such as phytochemicals, examples are curcumin, resveratrol and ginseng can aid with the anti-inflammatory, antioxidant and microbiota modulation but there is low bio availability. Photobiomodulation (Light Therapy) where the light is applied to the gut, altering the microbiota composition and increasing the SCFA-producing bacteria. Future orientated therapies are psychobiotics which affect the brain function and microbiome engineering. With so many therapeutic interventions available there are also many

limitations, as the microbial composition differs in every individual by diet, genetics or geography so there is a need for personalized medicine and there is still an unresolved discovery if dysbiosis causes the disease or results from it. Moreover, identifying specific microbial species and mapping signalling pathways remains a significant challenge. In addition, neurodegeneration is largely irreversible, inferring that late diagnosis makes it difficult to reverse neuronal damage. Successful future directions inculcate personalized medicines based on the unique microbiome profiles, multi-omics approaches like metagenomics and metabolomics, to identify the microbial species and functional pathways. Usage of the microbiome based biomarkers for early detections and microbiome engineering for genetically modifying bacteria and targeted therapeutic delivery (Izzeddine et al)53 (Li et al)54.

Conclusion

To sum it all up, the evidence presented in the entirety of the paper, emphasizes the pivotal role of gut microbiota in the pathophysiology of neurodegenerative diseases impacting the immune function, intestinal barrier integrity, and neuroinflammatory processes. The initiation and continuity of the barrier disruption, neuroinflammation and microbial imbalance caused by gut dysbiosis favours neuronal damage via gut-brain axis. This mechanism thrives by the reduction of the beneficial microbial metabolites such as SCFAs and the rise in the presence of pro-inflammatory mediators like LPS which contributes to microglial overactivation and blood–brain barrier dysfunction. The association between gut microbiota imbalance and neurodegeneration is strongly supported by the existing findings but the relationship remains to be fully established. The variability between individuals and the incomplete mechanistic understandings limit the therapeutic approaches targeting the microbiome which exhibits positive results. Upcoming research should be dedicated to personalized medicine, longitudinal studies, and advanced multi-omics approaches to clarify underlying mechanisms and develop targeted interventions. Ultimately, the mitigation of the neurodegenerative diseases can be executed by the promising strategy of maintaining the gut microbial homeostasis.

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