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REVIEW ARTICLE

The intestinal microbiome and Alzheimer's disease: A review

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Abstract

Alzheimer's disease (AD) is an increasingly common neurodegenerative disease. Since the intestinal microbiome is closely related to nervous system diseases, alterations in the composition of intestinal microbiota could potentially contribute to the pathophysiology of AD. However, how the initial interactions with intestinal microbes alter events later in life, such as during neurodegenerative diseases, is still unclear. This review summarizes what is known about the relationship between the intestinal microbiome and AD.

KEYWORDS
Alzheimer's disease, blood-brain barrier, intestinal barrier, intestinal microbiota, neuroinflammation

1 | INTRODUCTION

Alzheimer's disease (AD) is the most common chronic neurodegenerative disease. Patients suffer from short-term memory loss, verbal memory decline, mood swings, and loss of motivation, planning and intellectual coordination skills.[1,2] AD is characterized by cortex atrophy, loss of neurons and synapses, amyloid plaques caused by the aggregation of Aβ1–42 peptide and neurofibrillary tangles formed by tau, a microtubule-associated protein. In addition to the deposition of Aβ and neurofibrillary tangles, neuroinflammation is also a pathological hallmark of AD.[3,4] Alarmingly, the number of individuals suffering from Alzheimer's disease has increased from 21.7 million to 46 million in a quarter century.[5] However, over 95% of cases are sporadic AD patients and the pathogenesis is still unclear. There are no effective curative treatments. The results of recent genome-wide association studies (GWAS) have identified and validated 20 novel AD genetic risk loci, such as the ABOEe4 allele, ABCA7, clusterin (CLU), fermitin family member 2 (FERMT2), phosphatidylinositol-binding clathrin assembly protein (PICALM),[6] but none of the markers are located within coding regions, suggesting a comparatively strong contribution of epigenetic or environmental factors to AD risk.[7] In humans, it is estimated that the microbiome encodes >100-fold more genes than the human genome[8] and is impacted by host and environmental factors. Recent studies indicate that there is a close correlation between the intestinal microbiome and AD, which raises a new hypothesis about the pathogenesis of AD. In this review, we will discuss what is known about the possible relationship between the intestinal microbiome and AD.

2 | COMPOSITION OF THE INTESTINAL MICROBIOME

Microbes are found throughout the human body[9] and the majority of metabolites in human plasma are microbe-derived.[10] The microbes residing in the body are classified into three groups: symbionts, commensal organisms and pathobionts.[11] Numerous small molecules synthesized by microbiota influence human health. The microflora take

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part in the regulation of many physiological functions, including synthesizing vitamins and amino acids, influencing the biotransformation of bile acids, increasing the bioavailability of minerals, forming a barrier against colonization by pathogenic bacteria and stimulating the production of substances that inhibit the adhesion of pathogens to enterocytes.[12,13]

The alimentary tract is the most substantial contributor to the total bacterial population within the human body,[9] and it is one of the largest interfaces (250-400 m^2) between the host and what can be regarded as a continuation of the external environment in the human body.[14] Simultaneously, intestinal mucosal lymphoid tissue is the largest and most important human immune organ, containing 70%-80% of the immune system in the whole body.[15] The human gastrointestinal tract is inhabited by nearly 10^{14} microorganisms from at least 1000 distinct microbial species which are collectively known as intestinal microbiota.[16] The cell density of human intestinal microbiota varies at different positions along the gastrointestinal tract, with 10^2/mL in the stomach, duodenum and jejunum, 10^3-10^8/mL in the ileum and 10^{12}/mL in the colon.[9,17] Almost the entire gut intestinal microbiome is composed of species from the phyla *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, *Actinobacteria* and *Verrucomicrobia*.[17] The composition of the microbiota differs in various regions of the digestive tract (Table 1). *Lactobacillaceae*, *Clostridum*, *Streptococcus Bacteroides*, *Actinomycinae*, *Corynebacteria* dominate in the small intestine, while the colon is colonized by *Bacteroides*, *Clostridum*, *Bifidobacterium* and *Enterobacteriaceae*.

The microbial composition of the intestinal tract is impacted by host and environmental factors, the mode of delivery at birth, the postnatal environment, diet, use of drugs, as well as age, sex, microflora transplantation and physiological influences, and holds distinctive compositional and functional features across different life periods.[18] The microbial community is relatively stable in adults, and starts to shift about 65 years of age, the age of predilection for AD.[14] It has been shown that the microbiome in the elderly population is less diverse and resilient, which makes it more susceptible to environmental factors and interventions than that of younger adults. Similarly, the intestinal microbiome of centenarians was found to differ significantly from that of other adults. Biagi and his team found that the genera *Coprococcus*, *Roseburia*, and *Faecalibacterium* were negatively correlated with age, while *Oscillospira* and *Akkermansia* had a positive age correlation.[19] Alterations in the intestinal microbiome are associated with the physical state of the elderly. The frail tend to have a decreasing abundance of *Lactobacilli*, *Bacteroides Prevotella* and *Faecalibacterium prausnitzii*, and increasing proportions of *Ruminococcus*, *Atopobium* and *Enterobacteriaceae*.[20]

TABLE 1 The composition of the microbiota in various regions of the digestive tract

Position	Density number/mL	Bacteria species
Stomach	0-10^2	*Lactobacillus*, *Candida*, *Streptococcus*, *Helicobacter pylori*, *Peptostreptococcus*
Duodenum	10^2	*Streptococcus*, *Lactobacillus*
Jejunum	10^2	*Streptococcus*, *Lactobacillus*
Proximal ileum	10^3	*Streptococcus*, *Lactobacillus*
Distal ileum	10^7-10^8	*Clostridum*, *Streptococcus*, *Bacteroides*, *Actinomycinae*, *Corynebacteria*
Colon	10^{11}-10^{12}	*Bacteroides*, *Clostridum* groups IV and XIV, *Bifidobacterium*, *Enterobacteriaceae*

3 | INTESTINAL MICROBIOME, NEURODEVELOPMENT AND NEUROINFLAMMATION

The Human Microbiome Project (HMP) is revealing the beneficial effects of intestinal microorganisms on human health.[20] Neurodevelopment is a complex process that is partly dependent on environmental signals from the intestines, which largely originate from the microbiome. The intestinal microbiome and its metabolites participate in neuroinflammation and basic neurogenerative processes such as the formation of the blood-brain barrier (BBB), myelination, neurogenesis, and microglia maturation, from the prenatal period to old age. The microbiota can influence neuroinflammation by modulating microglia and astrocytes. During maturation, microglia remain in an immature status in the absence of microbiota and can be rescued by the administration of short-chain fatty acids (SCFAs).[21] *Lactobacillus reuteri* can suppress neuroinflammation in astrocytes in the brain by promoting the production of indole-3-aldehyde and indole-3-propionic acid, which are then transported across the BBB.[22]

The BBB is formed by capillary endothelial cells, astrocytes, and pericytes and develops during the early period of intrauterine life.[23] It is the gateway for the passage and exchange of molecules and nutrients between the circulatory system and the brain parenchyma. Intestinal microbiota impact the permeability of the BBB during gestation, and the effects are propagated throughout life. Germ-free mice displayed increased BBB permeability compared to pathogen-free mice with normal intestinal flora,[24] and increasing BBB permeability may facilitate an increased rate of pathogen entry into the brain, allowing for neuroinflammation.[25] Microbial signals have been found to reduce the rates of neurogenesis very early in life during cortical development,[26] but rescue decreasing neurogenesis in the hippocampi of adult mice undergoing long-term antibiotic treatment.[27] Bacterial cell wall components also induce the proliferation of neurons in the frontal cortex.[28] The microbiome is also necessary for the regulation of myelin-related genes, with clear implications for cortical myelination, which is a critical process in the development of a healthy brain.[29] In addition to their effects on the central nervous system, intestinal microbiota regulate the enteric nervous system (ENS) and their effects depend on vagus nerve and myenteric neuron activities.[30] The ENS degenerates with age. Cholinergic nerves, as well as enteric glial cells, are lost in both the myenteric and the submucosal plexus.[31]

Metabolites produced by intestinal microbes are important molecules for neurological function. γ-Aminobutyric acid (GABA), the chief inhibitory neurotransmitter in the mammalian central nervous system, can be produced by *Lactobacillus* and *Bifidobacterium* species.

It plays an important role in developing brain. As an excitatory transmitter, GABA improves the intracellular Ca^{2+} concentration of postsynaptic neurons in the early stages of CNS development. GABA also takes part in the proliferation and development of neural progenitor cells via brain-derived neurotrophic factor (BDNF) and the formation of synapses,[32] and after development, it acts as an inhibitory transmitter by decreasing the intracellular Cl^- concentration.[33] In addition, GABA has been shown to suppress inflammatory immune responses in type 1 diabetes animal models,[34] and lower numbers of enteric *Lactobacillus* and *Bifidobacterium* decrease the amount of GABA in the intestines and CNS.[12]

Intestinal microbiota play an important role in the synthesis of serotonin (5-hydroxytryptamine, 5-HT),[35] which in turn plays a crucial role in the regulation of cognitive function. 5-HT is produced in the enteric nervous system of gastrointestinal tract and central nervous system. It regulates intestinal movements, mood, appetite, and sleep. It is also associated with memory and learning. Gut microbiota indirectly control the production of neurotransmitters by stimulating host enterochromaffin (EC) cells to produce 5-HT.[36] *Escherichia*, *Bacillus*, and *Saccharomyces* spp. can produce norepinephrine and dopamine.[30] Short-chain fatty- acids (SCFAs) are produced by probiotics in the colon, chief among them being acetic, propionic, butyric and lactic acids.[36]

Among the SCFAs, butyrate has received particular attention due to its beneficial effects on maintaining health. In fact, butyrate which is produced by *Butyricicoccus* and *Clostridium*, is the main energy source of colonocytes.[37] It increases the mitochondrial respiration rate and ATP production. Butyrate is a histone deacetylase inhibitor that induces the sprouting of dendrites, increases the number of synapses, and reinstates learning behavior and access to long-term memories.[38,39] Butyrate can facilitate increased gut intestine motility by stimulating cholinergic neurons of the ENS, whereas propionate decreases motility and increases secretion.

In addition to their role in neuroinflammation, commensal microbiota are closely connected to the systemic inflammatory responses of the host. It has been shown that germ-free animals show lack of growth of CD4 + T-cell populations. The intestinal microbiome stimulates epithelial cells and gut mucosal lymphoid tissue to release serum amyloid A1, and also stimulates the T-cell compartment and upregulates innate intestinal defense mediators. Particular bacterial strains, such as *Akkermansia muciniphila* and *Faecalibacterium prausnitzii* also possess anti-inflammatory properties,[14] and butyrate acts as an anti-inflammatory agent by suppressing the nuclear factor kappa-light-chain-enhancer of the signaling pathways of activated B cells (NF-κB).[40] It is also a potent agonist of the G protein-coupled receptors (GPRs), including free fatty acid receptor 2 (FFAR2), FFAR3 and GPR109. FFAR3 is highly expressed in the sympathetic nervous system and is associated with inhibiting ganglia activity,[41] and can promote the development of dendritic and T-cell precursors from bone marrow. GPR109A promotes the generation of Treg cells.[22] Microbial dysbiosis and increased intestinal permeability trigger systemic inflammation by elevating the levels of serum interleukin 6 (IL-6),[42] and IL-6 also increases in the serum and brain tissue of AD patients.[43]

4 | NEURONFLAMMATION AND AD

It has been demonstrated that both acute and chronic systemic inflammation are associated with an increase in cognitive decline in AD patients.[44] The classical pro-inflammatory cytokine tumor necrosis factor α (TNF-α) is produced by microglia and is an early cellular marker of AD pathology, and has also been shown to induce neuronal cell cycle events.[45]

Microglia and astrocytes are important players in the development and progression of neuroinflammation and are critical for the maintenance of normal brain homeostasis. Microglia located throughout the brain and spine account for about 15% of the neuroglia in the brain.[46] Microglia can clean up Aβ fibrils via phagocytosis. They surround amyloid plaques, and the presence of Aβ deposits in activated microglia in the brains of AD patients has been shown.[43] However, chronic neuroinflammation caused by the accumulation of Aβ and neuronal debris can damage the BBB, which induces the activated microglia to release pro-inflammatory cytokines.[47,48] In AD, the induction of an inflammatory response by microglia may influence neuronal integrity and function and contribute to neurodegeneration. Under inflammatory conditions, cytokines upregulate β-secretase mRNA protein and increase NF-κB signaling by activating TNF-α, resulting in increased Aβ production, which has a neurotoxic effect.[43]

Astrocytes also play a role in the progression of AD. Reactive astrocytes, as well as reactive microglia, contribute to neuroinflammation and BBB dysfunction. They also induce a pro-inflammatory profile, interacting with Aβ.[49] The accumulation of activated astrocytes correlates strongly with Braak staging in AD.[50,51] Moreover, metabolic alterations in neuronal and glial cells and the disruption of calcium homeostasis in neurons and astrocytes induce large-scale neuroinflammation and the loss of neurons, which is associated with hypervascularity and hyperpermeability.[52]

Recognition of the inflammatory hypothesis of AD has been gradually accepted over recent years. Some pathogens are associated with most of the changes seen in AD, such as inflammation, brain cell atrophy, immunological aberrations, amyloidogenesis, altered gene expression and cognitive deficits.[7] The Aβ peptide is a cleavage product generated by β- and γ-secretases, derived from Aβ protein precursor distributed in the neuronal membrane. Aβ42 peptides form the central core of senile plaques.[53] Consideration has been given to possible physiological roles of Aβ as an antimicrobial peptide (AMP), utilizing fibrillation to protect the host from a wide range of infectious agents.[54]

It has been reported that AD brains contain higher bacterial levels than the brains of non-demented controls.[55] An estimated 90% of Aβ plaques in AD patients' brains contained HSV-1 (herpes simplex virus) DNA.[56] Moreover, the risk of dementia increased 2.56-fold in patients with HSV.[57] Human herpes viruses 6A and 7 (HHV-6A, HHV-7) were also found to be abundant in the lobes of AD patients. These viruses interact with many of the known AD risk genes, including γ-secretase subunit presenilin-1 (PSEN1), BACE1, amyloid β precursor protein binding family B member 2 (APBB2),

CLU, bridging integrator 1 (BIN1), and PICALM.[58] Moreover, they showed a correlation with neuron loss.[58] Similarly, postmortem investigations showed the presence of *Chlamydia pneumoniae* in the brains of AD patients.[59] Aβ deposition has also been found in olfactory bulbs infiltrated by *Chlamydia pneumonia*.[60] Some observations suggest AD may also be associated with *Helicobacter pylori* and *Toxoplasma gondii* infection.[61,62]

Clinical anti-Aβ trials also found an increased incidence of infections, including meningoencephalitis,[63] orolabial herpes, skin infections[64] and upper respiratory infections,[65] among the study participants. The main pathways of pathogen infiltration of the CNS include the lymphatic pathways,[66] the BBB and the blood-labyrinth barrier (BLB).[67] Lymphatic vessels are spread along the transverse sinuses and superior sagittal sinus (SSS) and reach the olfactory bulb.[68] The entorhinal cortex-hippocampus axis and the olfactory system have been suggested as the earliest anatomical regions targeted by AD.[69] Accordingly, amyloid deposits can be found in the brains of non-transgenic BALB/c mice following intranasal infection with *Chlamydia pneumonia*.[60]

The BBB is also responsible for the strict control of the molecules transported into the brain. The increase in BBB permeability seen during physiological aging may facilitate an increased rate of pathogen entry into the brain.[25] This implies that age is a potential risk factor of Alzheimer's disease, and the intestinal microbiome may be responsible for pathogen infection in the brain and AD by changing the permeability of BBB.

Taken together, these studies suggest that microglial priming can affect brain development and, later, the onset and progression of neurodegenerative diseases. It has been found that the incidence of AD is reduced in patients who use nonsteroidal anti-inflammatory drugs (NSAIDs).[70]

5 | INTESTINAL MICROBIOME ALTERATIONS AND AD

Dysbiosis of the intestinal microbiome has been implicated in multiple diseases, including intestinal disorders and extra-intestinal disorders such as inflammatory bowel disease, diabetes mellitus, asthma, obesity, autism and rheumatoid arthritis.[13] Recent studies have also linked microbial dysbiosis to neurodegenerative disease.[71–73] A small number of studies have demonstrated different intestinal microbial populations both in human patients and in animal models of AD (Table 2). Observations of the microbiota of AD patients at the phylum level indicate that these participants harbor decreased numbers of *Firmicutes* and *Actinobacteria*, and an increase in *Bacteroidetes* compared to controls. Within the *Firmicutes*, the families *Ruminococcaceae*, *Turicibacteraceae*, *Clostridiaceae*, and *Clostridium sensu stricto* were all less abundant in AD patients.[74] Recent reports indicate similar alterations in animal models of AD. For example, $APP^{swe}/PS1^{\Delta E9}$ (PAP) transgenic mice had less *Firmicutes* but more *Bacteroidetes*.[72] These intestinal microbial alterations in AD animal models are associated with chronic neuroinflammation.

Neuroinflammation triggered by pro-inflammatory molecules causes increased permeability of the BBB,[75,76] resulting in immune cell infiltration, exacerbation of the inflammatory response, leading to reactive gliosis, and eventually causing neurodegeneration.[77] *Bacteroidetes* is a family of Gram-negative bacteria, and thus have lipopolysaccharide (LPS) as the major outer membrane component, which can trigger systemic inflammation and promote the release of pro-inflammatory cytokines.[78] Injection of LPS during brain development enhances microglial activity and results in increased levels of the pro-inflammatory cytokines IL-1β, IL-6 and TNF-α.[79,80] Additionally, LPS is associated with AD pathology, since it can potentiate amyloid fibrillogenesis when co-incubated with Aβ peptide,[81] and systemic injection of LPS in animals results in amyloid deposition and tau-related pathology.[81,82] In humans, LPS and Gram-negative *Escherichia coli* fragments have been found to co-localize with amyloid plaques in the brains of AD patients, and the levels of LPS and Gram-negative *E. coli* fragments were greater in AD patients compared to control brains.[83] Antibiotic exposure in pregnancy can reduce postnatal production of granulocyte colony stimulating factor (G-CSF), which has neuroprotective effects, promoting neural tissue repair and improvement in functional recovery.[84] Additionally, G-CSF has played a protective role in spatial learning and memory formation in animal models.[85,86]

Animal studies showed that *Akkermansia* and seven other bacterial genera were correlated with the levels of cerebral soluble Aβ42.[72] *Akkermansia* and *Butyricicoccus*, which can increase gut barrier integrity,[87] were negatively correlated with the amount of pathogenic Aβ42 in the brain. *Akkermansia* is involved in intestinal

TABLE 2 Altered composition of intestinal microbiota of AD patients and animal models of AD

	Increased numbers of microbiota	Decreased numbers of microbiota
AD patients	*Bacteroidetes*, *Proteobacteria*, *Bilopila*, *Bacteroidaceae*, *Gemellaceae*, *Rikenellaceae*, *Bacteroides*, *Phascolarctobacterium*, *Gemella*, *Alistipes*, *Blautia*	*Firmicutes*, *Actinobacteria*, *Ruminococcaceae*, *Turicibacteraceae*, *Peptostreptococcaceae*, *Clostridiaceae*, *Mogibacteriaceae*, *Bifidobacteriaceae*, *Erysipdotrichaceae* CC115, *Clostridiaceae* SMB53, *Dialister*, *Clostridium*, *Bifidobacterium*, *Turicibacter*, *Bifidobacterium*, *Adlereutzia*
PAP transgenic mice	*Tenericutes*, *Proteobacteria*, *Veriucomicrobia*, *Erysipelotrichales*, *Erysipeiotrichaceae*, *Rikenellacaea* unclassified genera	*Verrucomicrobia*, *Proteoacteria*, *Ruminococcus*, *Butyricicoccus*, *Allobaculum*, *Akkermansia*
5xFAD mice	*Firmicutes*, *Clostridium leptum*	*Bacteroidetes*

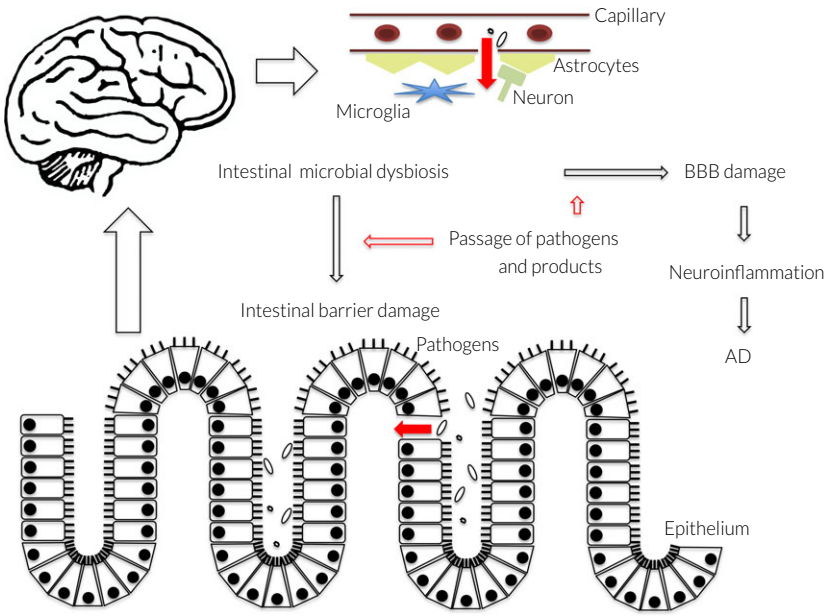

FIGURE 1 The potential relationship between intestinal microbiome alterations, mucosal barrier dysfunction, neuroinflammation and the pathogenesis of AD. Dysbiosis of the intestinal microbiome facilitates intestinal barrier and BBB damage and the entry of pathogens and their products into the circulatory system. Pathogens and their products pass into the brain via damaged BBB, and may intensify inflammatory reactions, and induce amyloid aggregation and the occurrence of AD

remodeling and controls the intestinal absorptive capacity.[88] *Butyricicoccus* produces butyrate, which is one of the SCFAs that drives the maturation of microglia and is needed for the maintenance of mature microglia.[21] It regulates the size and function of the colonic Treg cell pool and protects against colitis by inhibiting NF-κB activation in colon cells.[89,90] Accordingly, a decrease in protection of the intestinal barrier may result in increased expression of inflammatory components and the influx of LPS into the AD brain. Consistent with this hypothesis, Leblhuber et al. found elevated fecal calprotectin levels in patients with AD, indicating a leaky intestinal barrier.[91] Thus, increased abundance of *Bacteroides* may result in increased translocation of LPS from the intestines into systemic circulation and the brain, and thus contribute to or exacerbate AD pathology. In human studies, postmortem examinations of the brains of AD patients showed increased histone deacetylase levels, which are associated with butyrate.[92] This may indicate a relationship between the decreased abundance of butyrate-producing bacteria and AD. Decreased amounts of enteric *Bifidobacterium* in PAP transgenic mice were found to be correlated with decreased levels of GABA, resulting in CNS dysfunction.[72] Moreover, a postmortem study showed that GABA levels were decreased in the cortices of AD patients.[93] Dysbiosis of intestinal microbes was also found to decrease the levels of brain-derived neurotrophic factor (BDNF) in the hippocampus and cortex, inducing cognitive disorders via the intestine-brain axis.[94]

At present, AD is thought to be associated with innate immunity. Several risk factors for AD, including aging, systemic infection, inflammation, obesity in middle life and brain trauma, all involve an activation of the innate immune system.[95,96] Furthermore, PAP transgenic mice raised in the absence of microbiota have less Aβ.[72,97] Recent studies have found Aβ deposition not only in the brain, but also in the intestinal villous stroma in PAP transgenic mice older than 5 months age and in 5xFAD mice, indicating considerable expression of human amyloid-β protein precursor (AβPP). This may be the reason for the shorter, sparser and irregularly arranged intestinal villi of PAP transgenic mice with altered intestinal microbiota.[73,98]

6 | THE INTESTINAL MUCOSAL BARRIER AND AD

The intestinal mucosal barrier is composed of the mucosal layer, intestinal epithelial layer and microbiota.[99] The mucosal layer consists of mucin molecules secreted by goblet cells and the secreted mucus prevents the direct contact of microorganisms with the epithelial layer.[100] Epithelial cells are held together by tight junction proteins including claudins, occludin, junctional adhesion molecules, and tricellulin. Microbiota indirectly support the integrity of the intestinal barrier by stimulating epithelial cell proliferation and producing SCFAs indirectly.[99] The pro-inflammatory cytokines TNF-α, IL-4, IL-6, and IL-13 are known to increase the permeability of intestinal epithelial cell monolayers, and this effect has been related to increased expression of claudin.[99]

An increase in gut dysbiosis and a disrupted intestinal mucosal barrier can allow the passage of microbes, microbial products, and foreign antigens into the body, resulting in activation of the immune system.[101] Notably, host-microbe interactions contribute to a broad range of extra-intestinal autoimmune and inflammatory diseases.[102] Experiments have shown that the increased colonic permeability that comes with age is due to age-associated remodeling of intestinal epithelial tight junction proteins. Accordingly, the dysbiosis of the intestinal barrier leads to geriatric vulnerability to gastrointestinal dysfunction.[103] Intestinal microbial alterations and intestinal barrier injury in animal models of AD are associated with several risk factors for AD, such as intestinal inflammation, stroke, diabetes and hypertension. The abundance of microbes belonging to the family *Erysipelotrichaceae* correlated with inflammatory bowel disease (IBD) and

showed a tendency to increase with age in PAP transgenic mice.[98,104] Moreover, it has been showed that diabetes is associated with intestinal barrier dysfunction. Hyperglycemia increases intestinal barrier permeability via alteration of tight and adherence junction integrity, resulting in systemic influx of microbial products and enhanced dissemination of enteric infection.[105]

Stroke and hypertension are also risk factors for AD. Dysbiosis of the intestinal microbiome has also been implicated in stroke, and is correlated with increasing vascular and epithelial permeability.[106] It has been showed that kidney cells and blood vessels express receptors for SCFAs and they are associated with hypertension. Moreover, the bacteria that show a decrease in numbers in the intestines of AD patients regulate blood pressure via their fermentation products.[107]

Exercise, which is an important factor that reduces the prevalence of AD, is also associated with the intestinal barrier. Intestinal mucosal damage partly arises from imbalances in pro-inflammatory and anti-inflammatory cytokines. Repeated exercise results in reduced pro-inflammatory cytokine expression and increased anti-inflammatory IL-10 expression.[108] One study has demonstrated that regular exercise can decrease colonic oxidative insult in a rat model of colitis.[109] Regular exercise also has an anti-inflammatory effect that improves the immunological profile in type 2 diabetes mellitus, coronary artery disease, peripheral arterial disease and obesity.[20]

There is a lack of evidence that the cognitive reserve is correlated with the intestinal barrier and intestinal microbes. However, it can the improve symptoms of AD in the elderly whose intestinal barrier and BBB have been injured already.[3]

7 | PROBIOTICS AND THERAPY

Probiotics and fecal microbiota transplantation have been used to treat intestinal disease, diabetes, neuropsychological diseases and multiple diseases in animal models and human patients.[110] The effects of probiotics include correcting gastrointestinal barrier defects and the composition of intestinal microbiota, reducing inflammation and releasing biogenic factors.[30] They can improve clinical symptoms, histological alterations and mucus production by reducing inflammation and are well tolerated, effective, and safe in patients with IBD.[111] Probiotics are also helpful in controlling blood glucose levels by affecting SIRT1 and fetuin-A levels to a certain extent.[112] Interestingly, recent studies found that probiotics had a beneficial impact on mental disorders. Dietary supplementation with *Bifidobacterium* cultures can correct behavioral deficits of rats in the forced swim test and elevate plasma tryptophan, a precursor of a highly potent neuroprotective antioxidant. Similarly, *Bacteroides fragilis* was found to be able to correct communication defects, anxiety-like behaviors and sensorimotor behaviors by decreasing the level of 4-ethylphenylsulfate. Oral administration of *Lactobacillus* and *Bifidobacterium* can improve mood and alleviate anxiety and depressive symptoms, as well as decrease urinary cortisol.[113] *Lactobacillus* has also been found to alleviate the gastrointestinal symptoms of people under stress, while also reducing the level of salivary cortisol.[114] It has been reported that the transplantation of fecal microbiota cured a patient with seizures and Crohn's disease, who remained without relapse for more than 20 months.[115]

8 | FUTURE DIRECTIONS

The pathogenesis of AD is still unclear. Current treatments that pursue the classical hypotheses of AD causation, such as the amyloid hypothesis, the tau hypothesis, and the cholinergic hypothesis, are ineffective. Intestinal microbiota influence human health and disease. An increasing number of scientific reports suggest an important role of the intestinal bacterial flora in multiple disorders. Notably, intestinal microbiota can promote the occurrence of neuropsychiatric disorders. Intestinal bacteria can also impact the function and structure of the brain via the intestine-brain axis. The intestinal microbiome and intestinal barrier are closely related to nervous system diseases, although the specific mechanisms remain unclear. Studies have shown that dysbiosis of intestinal microbiota can induce brain pathology. The intestinal barrier and BBB, as the main protectors against pathogen infection, may play a crucial role in the pathogenesis of AD. The increasing permeability of the intestinal mucosa and BBB in the elderly may intensify inflammatory reactions, and induce amyloid aggregation. Moreover, dysbiosis of the intestinal microbiome facilitates the entry of LPS and pathogens into the circulatory system and CNS, which in turn may lead to a vicious cycle of neuronal destruction (Figure 1). Thus, in the future, we might find biomarkers associated with intestinal microbes and inflammation that can be used for early diagnosis and prevention of AD by treating neuroinflammation, improving the intestinal barrier, and regulating the microbiome. However, such progress is predicated on a better understanding of the bidirectional communication between the brain and microbiota, which should be a focus of future research.

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CONFLICT OF INTEREST

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