ORIGINAL ARTICLE

The Potential Role of Intestinal Macrophages in the Gut-Brain Axis

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Abstract: Intestinal macrophages are crucial for maintaining gastrointestinal (GI) homeostasis and also contribute to various inflammatory disorders within the gut. As the most abundant immune cells in the GI tract, intestinal macrophages perform multifaceted functions. These include balancing immune responses to either innocuous antigens or harmful stimuli, supporting mucosal barrier integrity, and affecting gut secretion and motility through interactions with the enteric nervous system (ENS) and other nerves. A complex communication system, known as the "gut-brain axis" (GBA), exists between the intestine and the central nervous system (CNS). It integrates multilevel signals and modulates the functions of these two organs. A myriad of studies have revealed that alterations in the enteric microbiota are linked to various CNS disorders, such as Alzheimer's disease, Parkinson's disease, brain malignancies, multiple sclerosis, stroke, stress, anxiety, depression, autism, and schizophrenia. The mechanisms underlying the impact of gut dysbiosis on neuroinflammatory and neuropsychiatric diseases involve microbial metabolites and products, neurotransmitters and neuropeptides, immune regulation (including cytokines and chemokines), and neuroendocrine pathways. Notably, the functional status of intestinal macrophages is highly sensitive to the composition of the microbiota and thus can regulate the progression of CNS diseases via the GBA. Intestinal macrophages are found throughout the GI tract and may communicate with the brain through the nervous, circulatory, and immune systems. Thus far, there are relatively few studies that have explored the cellular and molecular mechanisms by which intestinal macrophages regulate CNS homeostasis and pathological conditions. The heterogeneity and niche-specific phenotypes of intestinal macrophages may have hindered a complete understanding of their specific roles in the context of homeostasis and disease. Here, we describe the progress made in understanding the distinct populations of intestinal macrophages and their roles in the GBA, providing an overview of their contributions to CNS homeostasis and dysfunction.

Keywords: Intestinal macrophages; Gut-brain axis; Central nervous system; Brain; Homeostasis; Microbiota.

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1. INTRODUCTION

The gastrointestinal (GI) tract holds the important function of absorbing nutrients and water, which are essential for sustaining life. This function relies on an intact barrier that not only segregates the

body from the external environment but also supports substance exchange. Simultaneously, akin to a shutter, this barrier is able to defend against the invasion of intestinal microorganisms. As such, the gut is equipped with a large reservoir of tissue macrophages, which, in coordination with other cells, ensure a delicate balance between tolerance to innocuous components and initiation of an immune attack against potentially harmful agents, such as pathogens and toxins. Intestinal macrophages are found residing throughout the various gut layers, including the mucosal and submucosal regions. They serve as "gatekeepers," maintaining the physical integrity of the epithelial barrier and detecting abnormal penetrations, such as microbes or bacteria-derived products. By working with other cells, including epithelium, enterochromaffin cells, neuropod cells, dendritic cells, lymphocytes, muscle cells, and neurons, intestinal macrophages can deliver messages throughout the GI tissue, joining a dense regulatory network that involves immune, endocrine, and neural connections. Hence, inappropriate immune responses or aberrant behaviors of intestinal macrophages are closely associated with many GI diseases, including inflammatory bowel disease (IBD), necrotizing enterocolitis, and colorectal cancer, as well as gut-related disorders such as neurodegeneration and neuropsychiatric diseases. Identifying how intestinal macrophages contribute to gut homeostasis and inflammation will be instrumental in developing new therapies for gut-associated diseases.

The GI tract is populated by a large microbial community that comprises bacteria, archaea, fungi, protozoa, and viruses (1-4). The co-evolution between the human body and gut microbes has established a symbiotic ecosystem in which the host allows the microbiota to colonize, while the microbiota assists the body in nutrient intake and waste excretion. Numerous studies have demonstrated that the microbiome in the intestine exerts a substantial influence on health, both in homeostasis and disease. Of note, the concept of the "gut-brain axis" (GBA) is widely recognized, highlighting the bidirectional communication between the gut microbiome and the central nervous system (CNS) (5, 6). The GBA is a complex information transmission network between the GI tract and the brain, activated by various factors, including the activities of the gut microbiota (Fig. 1). It involves multiple regulatory pathways, including innate and adaptive immune responses, the autonomic and enteric nervous system (ENS), vagus and spinal nerves, the neuroendocrine system, the hypothalamic-pituitary-adrenal (HPA) axis, and the circulatory system (6-8). Primary signaling events that modulate brain function are initiated by compounds released by gut microbiota, including metabolites and microbe-derived products (9). Among these chemicals, some, such as lipopolysaccharide (LPS), can directly activate the immune system in the gut or affect CNS immunity through the circulatory system (10, 11). They have been shown to regulate microglial activation and neuroinflammation and are associated with neurological disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis (10, 11). Several metabolites, including vitamins, bile acids, short-chain fatty acids (SCFAs), and amino acids as well as their derivatives, have been reported to regulate gut-brain signaling through many pathways (7, 8, 12, 13). Abnormalities in their processing are linked to a broad spectrum of neurodegenerative and psychiatric disorders, including AD, PD, Huntington's disease (HD), brain injury, stroke, amyotrophic lateral sclerosis, schizophrenia, autism, stress, and depression (5, 12, 14-20). However, the precise mechanisms by which these compounds influence the GBA remain largely unknown. In addition, studies have shown that gut microbiota can produce or induce enterochromaffin or neuropod cells to release neurotransmitters, such as dopamine, acetylcholine, histamine, melatonin, γ-aminobutyric acid (GABA), and serotonin (21-23). These neuroactive molecules have been revealed to play important roles in brain-related diseases (6, 22, 23). Especially, the gut produces most of the body's dopamine and serotonin, both of which are essential for brain function (22). Yet, the manner in which these molecules modulate the CNS via the GBA requires further investigation, particularly because of their short half-lives and limited ability to cross the blood-brain barrier (BBB). In preclinical animal models, potential mechanisms of gut-brain communication in brain pathogenesis involve signaling pathways linked to the immune, nervous, and neuroendocrine systems (24-26). Overall, changes in the diversity or relative abundance of the gut microbiota may alter the levels of microbe-derived compounds, which can subsequently perturb brain physiology through multiple pathways of the GBA.

However, to date, there is a limited understanding of what truly constitutes a healthy adult gut microbial profile, and to what extent alterations in

microbiota composition could lead to pathological changes. This uncertainty is due to the wide variety of species in the microbiome and the distinct functional capacities of each category across individuals (1, 27). A large body of research has focused on how intestinal microbiota influences host metabolism, highlighting its involvement in fundamental metabolic pathways and the pathogenesis of common metabolic diseases such as diabetes, obesity, and non-alcoholic liver disease (28). In particular, thanks to the development of metagenomic techniques and computational platforms for metabolic reconstruction, preliminary data on the metabolic capabilities of different bacterial species in the gut microbiome are now available (29, 30). Accordingly, microbiota-based interventions aimed at improving host metabolic health have been recommended. These strategies include the adjustment of diet and exercise, the administration of prebiotics or probiotics, microbiota transplantation, and the use of genetically modified microorganisms (28). Currently, although these interventions seem promising, it should not be overlooked that their therapeutic benefits in patients require long-term clinical observation for validation. In contrast, immunotherapies that target the gut ecosystem usually lead to a quick onset of effects and are used to treat a variety of gut-related diseases. Intestinal macrophages, the primary components of the innate immune system in the gut, can recognize, respond to, and tolerate microbes and their derived products. In turn, the composition and abundance of bacteria in the gut lumen can influence macrophage development and phenotypic states (24, 25). Therapies aimed at remodeling the phenotype of intestinal macrophages have been proposed as a treatment for IBD and may hold significant potential in addressing gut-related brain diseases. Importantly, evidence suggests that intestinal macrophages may play an essential role in the GBA by linking immune responses to nervous or neuroendocrine pathways (25, 26). In this work, we integrate recent advances in understanding the characteristics of intestinal macrophages with their potential contributions to neurological disorders.

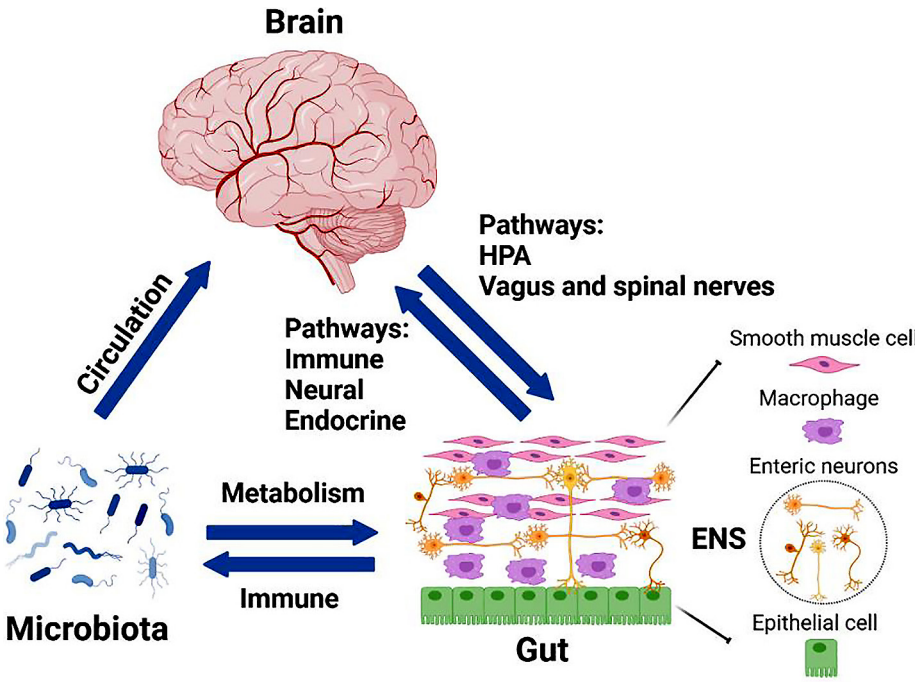

Figure 1. The gut-brain axis. HPA: hypothalamic-pituitary-adrenal; ENS: enteric nervous system.

2. ORIGIN AND CLASSIFICATION OF INTESTINAL MACROPHAGES

Microbial detection by the host is mediated by the immune system. At the frontline of host immunity, innate immune cells express a class of germ-line encoded pattern recognition receptors (PRRs) to surveil microbial activities in the environment (31). Pathogen-associated molecular patterns (PAMPs) are evolutionarily conserved structures found

across similar types of microorganisms (32, 33). PAMPs are critical for microbial survival and are not normally found in host cells (32, 33). Innate immune cells respond to microbes and their products through interactions between PRRs and PAMPs (33, 34). In addition, under some circumstances, host components such as proteins or lipids from damaged cells can also be recognized by PRRs to induce immune responses (35). These molecules are known as damage-associated molecular patterns (DAMPs), which convey messages of tissue injury or pathogen infection in the local environment (36, 37). Macrophages, which are typical innate immune cells, express a multitude of PRRs, including Toll-like receptors (TLRs), nucleotide oligomerization domain (NOD)-like receptors (NLRs), retinoic acid-inducible gene-I (RIG-I)-like receptors (RLRs), C-type lectin receptors (CLRs), and absent in melanoma-2 (AIM2)-like receptors (ALRs) (38, 39). In the intestine, the number of macrophages far exceeds that of other innate cells. Intestinal macrophages (Fig. 2), present throughout the gut, are heterogeneous and exhibit functional diversity based on their anatomical location (40-42). Depending on their PRRs, they monitor the gut microbiota constantly. The most well-defined role of intestinal macrophages is to help establish immune equilibrium in the mucosal layer, balancing microbiota tolerance and microbial removal (41, 42). Alterations in gut microbiota or macrophage populations that result in the breakdown of this equilibrium can lead to disorders in both the gut (24, 41, 43, 44) and the brain (5-9, 25) (Table 1). The mechanisms regulating this equilibrium involve the differentiation and maturation of intestinal macrophages, as well as their interactions with other cells (25, 45-48).

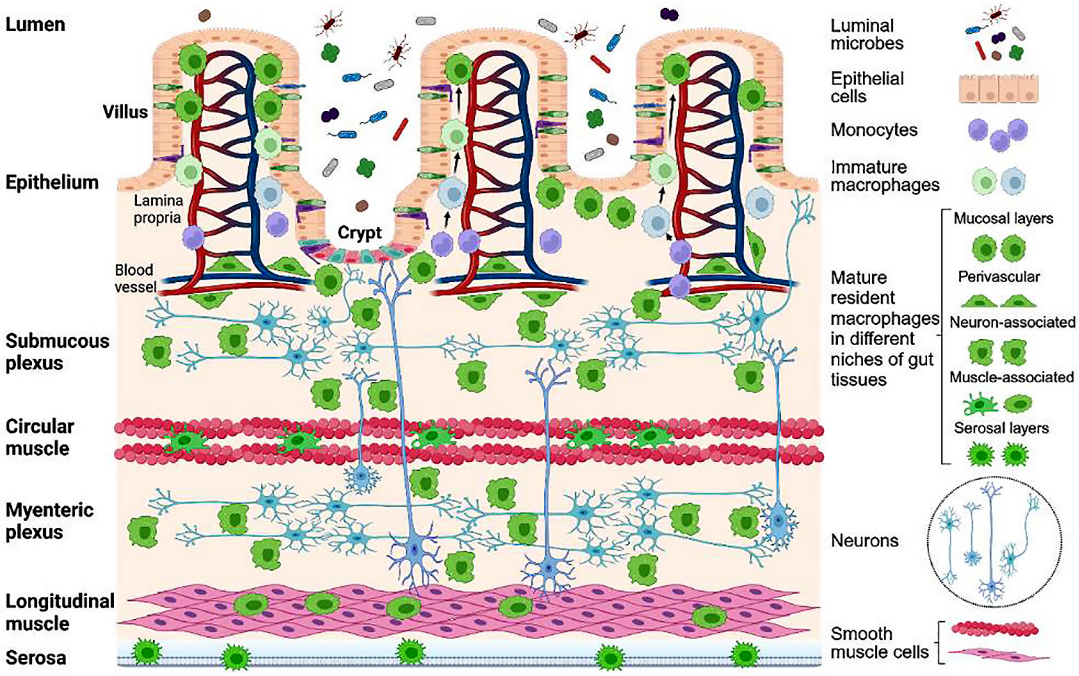

Figure 2. The layer-specific colonization of intestinal macrophages. Intestinal macrophages (green) are located throughout all layers of the gut wall, including the mucosa, submucosa, muscularis, and serosa. According to niche specificity, intestinal macrophages primarily include the main subpopulation located within the mucosal lamina propria (small intestine and colon), as well as other subpopulations associated with neurons, smooth muscle cells, or blood vessels. Lamina propria macrophages are continually replenished by blood monocytes that undergo a cascade of differentiation before maturation, commonly referred to as the monocyte 'waterfall'. Macrophages in deeper layers, such as the submucosa and muscularis externa, are derived from both embryonic precursors and blood monocytes and have a slower turnover rate. Most macrophages associated with neurons, muscles, and blood vessels can maintain themselves through self-renewal. Macrophages interact with various cells to support intestinal homeostasis.

Subtype	Niche	Location	Origin	Phenotype	Function	Disease	References
Lamina propria macrophages	Lamina propria	Mucosal layers (small intestine and colon)	Blood monocytes (bone marrow)	**1.** Mature macrophages: Cx3CR1^{hi} MHCII^{hi} CD64^{+} (mouse); CD14^{lo} CCR2^{-} CD11C^{lo} (human) **2.** Inflammatory macrophages: Cx3CR1^{int} MHCII^{hi} CD64^{+} (mouse)	**1.** Maintaining the epithelial barrier **2.** Inducing immune tolerance to both food and symbiotic microorganism 3. Mediating anti-inflammatory or proinflammatory responses	**1.** IBD, irritable bowel syndrome, colon cancer, sepsis **2.** Intestinal disorders associated with AD, PD, HD, anxiety, depression, autism, TBI	43, 56, 57, 63, 72, 74, 80, 84, 85, 86, 87, 88, 89, 144, 145, 146, 153, 159, 160, 162, 164, 165 168, 169, 174, 175, 182, 184, 185, 186, 187, 192, 196, 198, 206
Neuron-associated macrophages	Submucosal and myenteric plexuses	Submucosal layers and muscularis externa (the gastrointestinal tract)	1. Blood monocytes (bone marrow) 2. Self-maintaining (embryonic origin)	Tim-4^{+} CD4^{+} MHCII^{+} CD163^{+} Transcriptome: *Tmem119, P2ry12, Siglech, Trem2, Olfml3*	**1.** Supporting the survival of enteric neurons **2.** Inhibiting inflammation **3.** Regulating gut secretion and motility	**1.** Postoperative ileus **2.** Intestinal dysmotility associated with AD, PD, HD, TBI	42, 60, 61, 107, 113, 115, 116, 121, 122, 124, 125, 126, 127, 147, 148, 150, 152, 176, 196, 199, 202
Muscle cell-associated macrophages	Circular and longitudinal muscles	muscularis externa (the gastrointestinal tract)	Self-maintaining (embryonic origin)	CX_3CR1^{+} TRPV4^{+} MHCII^{+} CD163^{+}	Regulating colon contraction to influence gut motility	**1.** Postoperative ileus **2.** Intestinal dysmotility associated with TBI	61, 65, 66, 107, 119, 128, 129, 196
Perivascular macrophages	Blood vessel (large veins and arteries, microvasculature)	Mucosal and submucosal layers (small intestine and colon)	**1.** Self-maintaining (embryonic origin) **2.** Blood monocytes (bone marrow)	**1.** Transcriptome: *Tnfaip2, Anpep, Ecm1, Hif1a,* and *Mmp2* **2.** Transcriptome: *Ccr2, Nr4a1* **3.** CD169^{+}	**1.** Maintaining vascular integrity and barrier function **2.** Microbial defense **3.** Phagocytosis, antigen presentation, and inducing immune tolerance		61, 68, 69, 133, 134

AD, Alzheimer's disease; PD, Parkinson's disease; HD, Huntington's disease; IBD, Inflammatory bowel disease; TBI, Traumatic brain injury

Table 1. Characteristics of intestinal macrophages.

2.1. Origin and maintenance

Like most tissue-resident macrophages, before birth, intestinal macrophages arise from macrophage precursors that develop in the embryonic yolk sac or fetal liver (49, 50). These primitive macrophages possess the self-proliferative capacity and constitute the prenatal macrophage population in the gut (50, 51). Into adulthood, most organs, including the liver, lungs, pancreas, kidneys, and adipose tissue, contain tissue-resident macrophages of dual origin: one subset originates from embryonic precursors, and the other subset derives from hematopoietic stem cells (HSCs) in the bone marrow (52, 53). After birth, HSCs continue to differentiate into $Ly6C^+$ monocytes, which can migrate through the bloodstream into multiple organs and develop into tissue-resident macrophages under both homeostatic (such as during tissue remodeling) and inflammatory conditions (52-55). However, earlier studies indicated that intestinal macrophages were an exception to this pattern, with their embryo-derived macrophages being continuously replaced by macrophages derived from circulating monocytes during adulthood (56-59). It has been controversial whether a small number of intestinal macrophages of embryonic origin persist in the adult intestine. Notably, recent studies in both mice and humans have demonstrated that several subsets of long-lived intestinal macrophages, existing in different areas of the gut, arise from embryonic precursors and maintain themselves through self-renewal (60-62). Thus, intestinal macrophages are highly heterogeneous and exhibit differential turnover rates. Moreover, a dynamic process known as the monocyte "waterfall" imprints these subpopulations of intestinal macrophages, which are short-lived and constantly induced in the gut (56, 63). In light of their phenotypes and origins, intestinal macrophages are frequently classified into three main categories: monocyte-derived mature macrophages, monocyte-derived inflammatory macrophages, and self-maintaining macrophages (41, 43). In addition, the newly described niche model proposes that macrophage identity is largely determined by local tissue-specific cues rather than the origin of the macrophages (64). Consequently, distinct populations of intestinal macrophages throughout the gut wall are now being more thoroughly investigated based on their specific niches, such as the mucosal lamina propria and the muscularis layers (42, 65, 66).

2.2. Subpopulations in specific niche

In the GI tract, macrophages occupy various niches and conduct diverse functions. Within the mucosal layer, the pool of macrophages is located in the lamina propria, a dense connective tissue that lies beneath the epithelium (42, 67). Lamina propria macrophages constitute the main body of intestinal macrophages and undertake the dual roles of host defense and antigen tolerance. Most macrophages in the lamina propria are derived from blood monocytes and have a short lifespan, while several subsets closely associated with blood vessels display different turnover rates (61, 68-70). In both the submucosa and muscularis layers, the majority of macrophages are found adjacent to the nervous system and blood vessels (65, 66). Additionally, some macrophages are found associated with smooth muscle cells in the muscularis layers (66). A few macrophages are also present in the serosal layer, which isolates the intestine from the peritoneal cavity (71). Moreover, macrophages can also be detected within intestinal lymphoid tissues, such as Peyer's patches and mesenteric lymph nodes. The position of macrophages in the intestine has profound effects on their phenotype and function. Specialized subsets of macrophages develop upon receiving unique instructions from the surrounding cells. In this discussion, we delve into the characteristics of these intestinal macrophage subsets with niche specificity and speculate on their contributions to intestinal physiopathology.

2.2.1. Lamina propria macrophages

In adults, the maintenance of the resident macrophage pool in the intestinal mucosa relies on continuous blood monocyte input. In mice, the entire process of the monocyte "waterfall" takes around 5-6 days, beginning with the extravasation of monocytes from the bloodstream (Fig. 2). Responding to local environmental cues such as colony-stimulating factor 1 (CSF-1), cytokines (TGF-β and IL-10), and microbial metabolites (such as SCFAs), migrated $Ly6C^+$ monocytes undergo a series of phenotypic and functional changes before fully maturing as tissue-resident macrophages in the intestinal lamina propria (43, 56, 57, 63, 72). In mice, by expressing molecules involved in cell migration and adhesion, such as CCR2, CD62L, VLA-1, and LFA-1, circulating monocytes are recruited into the intestine and initially exhibit a phenotype of

Ly6C^{hi} CX$_3$CR1^{int} MHCII$^-$ (P1) (72). These cells first acquire the expression of MHCII (P2), then downregulate the levels of Ly6C and other proteins responsible for monocyte migration (P3), and finally evolve into mature resident macrophages (P4) by increasing the expression of CX$_3$CR1, F4/80, and CD64 (56, 57, 72). A similar process of macrophage development occurs in the human intestinal mucosa (Fig. 2), where classical CD14^{hi} CCR2$^+$ CD11C^{hi} monocytes progressively transition through several intermediate states before ultimately converting into CD14^{lo} CCR2$^-$ CD11C^{lo} intestinal resident macrophages (56, 62, 73). Interestingly, unlike mature lamina propria macrophages in mice, human monocyte-derived macrophages demonstrate extremely low levels of CX$_3$CR1 (73). Notably, under the influence of environmental cues, including continuous exposure to commensal microbiota, dietary antigens, and anti-inflammatory cytokines (TGF-β and IL-10), this progressive phenotypic transition of blood monocytes leads to the generation of mature macrophages (P4) that typically function in resolving inflammation (72, 74). Mature lamina propria macrophages are pivotal in maintaining the epithelial barrier and promoting immune tolerance to both food antigens and symbiotic microorganisms. In general, they exhibit enhanced phagocytic activity, increased secretion of anti-inflammatory cytokines such as IL-10, and reduced production of proinflammatory mediators, including IL-6 and inducible nitric oxide synthase (iNOS) (75-77). Additionally, they show low responsiveness to PRR ligands but actively facilitate monocyte recruitment (56, 57, 76). These functions align with the characteristics of the intestinal mucosa, which exhibits physiological inflammatory anergy yet remains capable of rapidly responding to abnormal signals through a constant influx of monocytes (78, 79). Once microbes invade the gut wall or the epithelial layer is damaged, recruited monocytes can rapidly differentiate into proinflammatory macrophages, which are more efficient at microbial killing than mature resident macrophages. These proinflammatory cells express lower levels of CX$_3$CR1 but produce large amounts of proinflammatory cytokines (47, 56, 80). For instance, in a mouse model of colitis, CX3CR1^{int} proinflammatory macrophages, rather than CX3CR1^{hi} resident macrophages, mediate bacterial clearance and influence the severity of inflammation (56). Furthermore, intimate interactions between lamina propria macrophages and epithelial cells orchestrate epithelial self-renewal and macrophage differentiation via multiple signaling pathways (81-83). Significantly, resident macrophages can clear accumulated apoptotic epithelial cells through the efferocytotic machinery (84, 85).

Altered monocyte-macrophage differentiation in the lamina propria or dysfunction in mature macrophages can lead to both spontaneous and infectious inflammation in the intestine, resulting in diseases such as IBD, irritable bowel syndrome, colon cancer, and sepsis (43, 44, 47, 80, 86-89). Furthermore, the gut microbiota has a significant impact on the development of lamina propria macrophages. In germ-free mice or specific pathogen-free (SPF) mice treated with broad-spectrum antibiotics, the number of monocyte-derived macrophages is markedly reduced (57, 60, 90), indicating that the microbiota plays a crucial role in the replenishment of these macrophages. Moreover, in cases of dysbiosis, the anatomical location of macrophage population changes, leading to an increased bacterial load in the blood (68, 70). The microbiota or its derivatives are essential for establishing the tolerogenic phenotype and trained immunity in lamina propria macrophages. Indeed, in germ-free mice, lamina propria macrophages show reduced production of IL-10 and IL-1β, as well as decreased responsiveness to TLR stimulation (91, 92). This deficiency of both IL-10 and IL-1β in the mucosal layers further alters the differentiation trajectories of recruited monocytes and CD4$^+$ T cells, leading to increased ratios of proinflammatory macrophages and Th1 cells, and reduced induction of Th17 and FoxP3$^+$ Tregs (regulatory T cells) (59, 91-95). Additionally, it has been proven that the microbiota regulates macrophage function in both direct and indirect ways. Microbial components such as LPS, peptidoglycans, nucleic acids, flagellin, and membrane vesicles can directly interact with macrophages by binding to PRRs (33, 34). Sustained PRR stimulation can lead to epigenetic changes in macrophage chromatin and decreased expression of adaptor proteins, which inhibit the induction of proinflammatory cytokines such as TNFα and IL-12 while enhancing macrophage adaptation to the local microenvironment (76, 78, 79, 86, 96). Interestingly, microbial metabolic products, such as SCFAs including propionate, acetate, and butyrate, as well as Aryl hydrocarbon receptor (AhR) ligands, can induce tolerogenic resident macrophages both directly and indirectly. In mice, SCFA depletion using antibiotics results in macrophage hyper-responsiveness to bacterial stimulation and T-cell dysfunction (97). However, treatment with

antibiotics supplemented with SCFA butyrate can restore macrophage tolerance and prevent excessive Th1 immune responses (97). Butyrate can downregulate LPS-induced secretion of proinflammatory mediators in mouse lamina propria macrophages by suppressing intracellular histone deacetylase (98). AhR ligands derived from digested food or the microbiome, such as indole derivatives, contribute to the crosstalk between macrophages and the epithelium (78, 99, 100). Both SCFAs and AhR ligands can directly regulate the development of the intestinal epithelium and promote epithelial cells to release TGF-β, which supports macrophage biology and function in the mucosa (99, 100). In conclusion, various environmental factors, through distinct signaling events, work together to regulate the development of monocyte-derived macrophages in the mucosa. Gut microbiota and diet composition have significant effects on macrophage behavior. Mucosal macrophages may play a vital role in various local and systemic diseases by monitoring gut barriers and microbial activities.

2.2.2. Neuron and muscle cell-associated macrophages

The GI tract is tightly regulated by an intricate neural network that includes nerve fibers originating from extrinsic neurons and the intrinsic ENS. Extrinsic neurons, which consist of both sensory and autonomic neurons, participate in the direct interplay between the gut and the CNS. Extrinsic sensory neurons mainly gather into the vagal ganglia (VG) and the dorsal root ganglia (DRG), transmitting signals from the GI tract to the brainstem and spinal cord, respectively (101, 102). Conversely, extrinsic autonomic neurons, including vagal efferent parasympathetic motor neurons and sympathetic neurons, are responsible for delivering instructions from the CNS to the gut (101, 102). Importantly, the ENS, entirely located within the gut wall, can function independently of any neural inputs from other nervous systems. As such, *ex vivo* gut segments can still generate certain neurogenic motor patterns despite having severed connections with both the brain and spinal cord (103). The ENS includes different types of neurons that work together to output complex intestinal behaviors. These neurons can generally be classified as afferent neurons, interneurons, excitatory and inhibitory motor neurons, secretomotor neurons, and vasodilator neurons (104). Structurally, enteric neurons are organized into two distinct ganglionated neuronal plexuses: the submucosal plexus within the submucosal layer, and the myenteric plexus located between the circular and longitudinal muscles of the muscular externa (105). Macrophage subpopulations found in close association with these plexuses in the intestine are known as neuron-associated macrophages (42, 61). Moreover, in the muscular layers, some macrophages are observed in proximity to smooth muscle cells (66, 106). In most cases, macrophage populations in the muscularis externa are collectively referred to as muscularis macrophages (MMs) (66, 107). In the GI tract, the neural network and immune cells have evolved to coordinate host responses, including gut secretion, motility, and immune defense (108). Notably, the gut microbiota can regulate intestinal physiology by modulating neuronal programming and maturation, as well as immune cell activation (109-111). It has been found that both immune cells and neurons can recognize microbes directly and indirectly (101, 102, 104, 108). The gut microbiome plays an important role in gut sensation and behaviors, including pain perception and motility (109-112). Interestingly, macrophage populations have been reported to be implicated in multiple GI pathologies through their interactions with neurons or microbes.

Submucosal macrophages occupy a niche that contains abundant ganglionated neurons and blood vessels. Unlike lamina propria macrophages, which are replenished by monocytes, over 90% of submucosal macrophages have an embryonic origin and maintain themselves through self-renewal (61). Self-maintaining macrophages are found to express Tim-4 and CD4, and their depletion causes the loss of submucosal neurons and vascular disorder (60, 61). Furthermore, neuron-associated macrophages exhibit a unique transcriptome distinct from those near blood vessels, suggesting a specialized function in supporting the nervous system (61). Strikingly, these neuron-associated macrophages express a considerable number of genes that are uniquely enriched in microglia, including microglial core signature genes such as *Tmem119*, *P2ry12*, *Siglech*, *Trem2*, and *Olfml3* (113). Furthermore, the submucosal plexus is crucial for regulating gut secretion in the GI tract (114). Studies have shown that selective depletion of neuron-associated macrophages in the submucosa induces neuronal apoptosis and abnormal intestinal secretion of luminal fluid (61, 115). Loss of submucosal neurons has been observed in patients with slow transit constipation (116).

Currently, few studies have addressed the mechanisms by which macrophages regulate gut secretion through interactions with submucosal neurons. However, it can be concluded that macrophages are, at the very least, vital for enteric neuronal survival. In addition, fluid movement is influenced by neuron-evoked ion transport and epithelial permeability (42, 61). IL-6, which is known to regulate both neuronal excitability and mucosal integrity, can be produced by both macrophages and submucosal neurons (117, 118). Therefore, in the submucosal layer, cytokines may be one of the main mediators facilitating macrophage-neuron communication, thereby regulating gut secretion.

More studies have focused on the macrophage subpopulation in the muscularis layers. Similar to submucosal macrophages, this subset primarily consists of self-maintaining cells derived from embryonic progenitors. However, it has been shown that selective depletion of self-renewing macrophages leads to an increased proportion of bone marrow-derived macrophages in this layer (61). In addition, recruited cells also display a neuron-associated phenotype with very few differentially expressed genes compared to long-lived, self-sustaining macrophages (66). Of interest, within the muscularis externa, neuron-associated macrophages have a stellate-like morphology, while macrophages near smooth muscle cells exhibit a bipolar morphology (65, 119). However, few studies have explored whether this morphological heterogeneity is associated with the transcriptional and functional specialization of macrophage subpopulations. Phenotypically, the total population of MMs shows high expression of MHCII, CD163, and CX_3CR1 (65, 107). Therefore, MMs are likely to play an anti-inflammatory role and participate in tissue homeostasis and repair.

Intriguingly, MMs have been confirmed to regulate intestinal motility through multiple mechanisms (65, 107, 120-129). The depletion of MMs disrupts gut peristalsis and promotes infection-induced neuronal death (65, 107, 120, 121). MMs have been shown to regulate gut motility by communicating with the intrinsic ENS (107, 120). During homeostasis, MMs secrete bone morphogenetic protein 2 (BMP2), which activates BMP receptor signaling in enteric neurons. These activated neurons then promote peristalsis by inducing smooth muscle contractions (107). Conversely, enteric neurons can sense cues from commensal microbes and secrete CSF1, which supports MM survival and niche adaptation (107). Furthermore, it has been shown that MMs phagocytose dying enteric neurons and neuronal debris (120). Aging promotes a decrease in anti-inflammatory MMs, which is associated with increased neuronal apoptosis and intestinal transit time, highlighting the importance of MMs in assisting the ENS in regulating gut motility (121). A recent study has revealed a new reciprocal cell-cell communication between the ENS and MMs, in which ENS-derived TGF-β induces a neuroprotective phenotype in MMs. In turn, MMs facilitate the normal development and maturation of the ENS (122). Disruption of TGF-β signaling leads to a reduction in neuroprotective MMs and subsequent impairment of intestinal motility (122). Similarly, MMs can also influence peristaltic activity by interacting with the extrinsic autonomic nervous system (ANS), which includes sympathetic and parasympathetic neurons (65, 123-127). As is known, parasympathetic neurons, primarily vagal efferent motor neurons in the brainstem, mediate excitatory functions that include the enhancement of gut motility, digestion, and secretion (101, 102). These motor neurons exert their immunomodulatory function primarily by releasing acetylcholine (ACh) to activate the cholinergic anti-inflammatory pathway (108, 123). MMs express the α7 nicotinic acetylcholine receptor (α7nAChR) and can, therefore, respond to ACh stimulation (123). Patients with postoperative ileus (POI) typically experience reduced or ceased GI motility after surgery. In a mouse model of POI, α7nAChR-positive MMs were found to be essential for the vagus nerve stimulation-induced improvements in intestinal inflammation and motility (124). Interestingly, the vagal efferent interacts directly with cholinergic myenteric neurons that are closely associated with MMs, suggesting a collaboration between parasympathetic and enteric neurons in modulating gut motility (124, 125). Additionally, in a POI model, *Ccr2*$^{-/-}$ mice showed reduced monocyte-derived macrophages in the muscularis layers and slower recovery from intestinal inflammation and dysmotility compared to wild-type mice (126), highlighting a common role for various MM subsets regardless of their origin. Sympathetic neurons, which perform functions such as slowing gut motility and secretion, also communicate with intestinal MMs. Gut dysbiosis resulting in infections in gut tissues can activate extrinsic sympathetic neural circuits to release norepinephrine, which can polarize MMs into neuroprotective phenotypes via the β2 adrenergic receptor pathway

(65). This sympathetic neuron-MM axis limits infection-induced enteric neuronal death and facilitates gut motility (127). Overall, these studies have indicated that MMs regulate gut motility through a variety of neuro-immune interactions.

Furthermore, MMs have been shown to regulate GI motility via direct interactions with smooth muscle cells (65, 128, 129). A subset of intestinal MMs, characterized by a bipolar shape, are distributed close to smooth muscle cells and may have direct cellular contact (65, 128). In a study, intestinal CX_3CR1^+ MMs were found to express the transient receptor potential vanilloid 4 (TRPV4) channel (129), which senses osmotic, mechanical, and chemical cues. Independent of neural inputs, TRPV4 activation in MMs triggers the release of prostaglandin E2 (PGE2), which induces colon contraction by activating smooth muscle cells via PGE2 receptor signaling (129). In addition, it has been revealed that intestinal macrophage behavior has a significant effect on smooth muscle physiology (106). In the intestine, eliminating macrophage populations with high arginase activity can reduce smooth muscle contractility but increase smooth muscle thickness (106).

Additionally, some macrophages within the muscularis externa are adjacent to interstitial cells of Cajal (ICCs), which are specialized pacemaker cells for GI movement (66, 128). Pathological conditions such as POI, which involve disturbed intestinal motility, also show damage and reduction in ICCs (130). Although several studies have shown that inflammatory states of intestinal macrophages are associated with the phenotype and function of ICCs (131, 132), direct interactions between MMs and ICCs in modulating gut peristalsis warrant further exploration.

2.2.3. Perivascular macrophages

In the gut wall, the mucosal layer is heavily vascularized, and a subset of blood vessel-associated macrophages has been identified (61). These perivascular macrophages reside at the interface between gut tissues and the circulatory system, contributing to the gut-vascular barrier. They function as immune sentinels and may also participate in material exchange between the gut and the bloodstream. Additionally, since resident macrophages in the lamina propria are rapidly replenished by blood monocytes, the origin and composition of perivascular macrophages are likely heterogeneous.

One subpopulation close to large veins and arteries in the lamina propria is self-maintaining and exhibits a specialized transcriptome, with high expression of genes associated with angiogenesis such as *Tnfaip2*, *Anpep, Ecm1*, *Hif1a*, and *Mmp2* (61). Depletion of these long-lived macrophages leads to the destruction of VE-cadherin$^+$ blood vessels and increased vascular permeability (61), highlighting their important role in maintaining vascular integrity and barrier function. They may functionally contribute to preventing the dissemination of luminal pathogens into the bloodstream. Intriguingly, a study has shown that a subset of perivascular macrophages, primarily located around the microvasculature within the villi, is tightly regulated by monocyte recruitment *(Ccr2)*, maturation *(Nr4a1)*, and luminal microbiota (68). These macrophages probably originate from the bone marrow, and their function depends on microbial exposure. In the steady state, they remain in contact with each other (68). However, in a state of dysbiosis (antibiotic treatment), these macrophages reduce their connections with neighboring cells, resulting in increased bacterial translocation into the blood (68). Therefore, different subpopulations of perivascular macrophages may possess distinct characteristics imprinted by their niche, which are vital for maintaining intestinal homeostasis. Furthermore, a subset of macrophages expressing $CD169^+$ has been identified in both the lymphoid tissue and lamina propria of the intestine (69, 70, 133). They were found close to lymphatic or blood vessels within the villi, but distant from the epithelium (69, 133). $CD169^+$ macrophages have been reported to be primarily present in secondary lymphoid organs and participate in several biological processes, such as capturing particulate materials through phagocytosis, antigen presentation, and inducing immune tolerance to harmless antigens (134). Accordingly, it is likely that intestinal $CD169^+$ macrophages associated with the vasculature play a role in immune responses to food antigens and in the surveillance of harmful agents entering the bloodstream. An investigation has shown that in the context of colitis, $CD169^+$ macrophages secrete CCL8 to recruit inflammatory monocytes, leading to exacerbated mucosal damage (69). The biology and specialized function of intestinal $CD169^+$ macrophages require further investigation, particularly their ontogeny, differentiation, and signaling pathways.

3. INTESTINAL MACROPHAGES IN GUT-BRAIN DISORDERS

Although intestinal macrophages have long been known as the housekeepers of the GI tract, growing evidence suggests that these cells perform a plethora of additional tasks that influence the pathophysiology of both the gut and the brain (Table 1). Intestinal macrophages can engage in multi-directional crosstalk with the CNS through various components of the GBA, including intestinal microbiota, the epithelial barrier, neurons, immune and enteroendocrine cells, and blood and lymphatic vessels. This complex communication can have wide-ranging effects on human health and disease, including inflammatory and neurological disorders (Fig. 3). A comprehensive understanding of how intestinal macrophages regulate the GBA will assist in developing therapeutic interventions in the gut for managing CNS diseases.

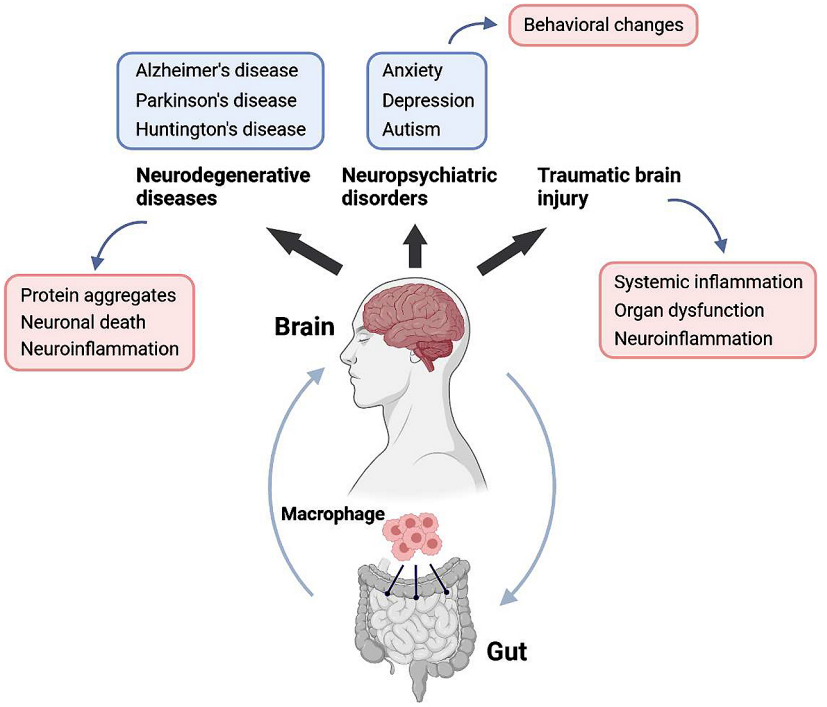

Figure 3. The activities of intestinal macrophages impact brain disorders. Intestinal macrophages likely participate in multi-directional crosstalk between the gut and the brain, influencing the progression of many neurological diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, stress, depression, and brain injuries.

3.1. Neurodegenerative diseases

As discussed previously, MMs regulate intestinal motility by releasing BMP2 to activate enteric neurons, while neuronal expression of CSF1 promotes the development of MMs (107). However, antibiotic treatment decreases GI motility and reduces the production of both CSF1 and BMP2 (107), suggesting that gut microbiota-driven communication coordinates macrophage-mediated immune regulation with neuronal activities. Notably, neurological disorders such as AD, PD, and HD show CNS progression and persistent gut dysfunction (135). Patients with neurodegenerative diseases (NDs) experience both brain- and gut-associated symptoms, including cognitive decline, abdominal pain, constipation, and diarrhea (136). Gut dysbiosis often manifests as abdominal pain and abnormal bowel movements (137). Recent studies have confirmed a strong correlation between gut dysbiosis and the incidence of NDs (6, 7). However, it remains unclear whether gut dysbiosis is a cause or an effect of CNS dysfunction. What is evident is that dysregulated intestinal homeostasis significantly influences the progression of NDs. Therefore, investigating how intestinal macrophages respond to dysbiosis and its subsequent effects on brain pathology would be highly valuable.

3.1.1. Alzheimer's disease

AD is the most common ND and mutations in genes such as amyloid precursor protein *(APP)* and presenilin 1 *(PSEN1)* are associated with its pathogenesis (138, 139). In the CNS, substantial neuronal loss is associated with excessive extracellular masses of amyloid β (Aβ) peptides and intracellular bundles of fibrillar Tau protein (54). Patients with AD frequently exhibit symptoms of intestinal inflammation, dysmotility, and dysbiosis (136, 140). Studies using animal models of AD have pinpointed the association between an altered gut microbiome and AD pathologies (141-144). Interestingly, a study has highlighted that in APP-mutated AD animals, chemically induced intestinal inflammation leads to increased plaque deposition in the CNS (144). Furthermore, an increased abundance of proinflammatory bacteria such as *Escherichia* and *Shigella* in the gut microbiome has been shown to promote brain amyloidosis (145). These bacterial species induce intestinal inflammation by stimulating innate immune cells, such as macrophages, to produce inflammatory mediators (145). Elevated blood levels of proinflammatory mediators such as IL-1β, CXCL2, and NLRP3 inflammasome are associated with increased plaque formation in the brain (145). Therefore, microbiota-dependent gut inflammation appears to play an important role in promoting Aβ pathology in the CNS. Moreover, an investigation has reported that AD mice, compared to healthy wild-type mice, exhibit significant loss of epithelial integrity, altered macrophage activity, and chronic intestinal and systemic inflammation (146). Transplantation of fecal microbiota from wild-type mice to AD mice reshapes the phenotype of both colonic macrophages and circulating inflammatory monocytes, resulting in reduced formation of Aβ plaques and Tau tangles, as well as cognitive improvement (146). In addition, APP is also expressed by both enteric neurons and macrophages. It has been found that AD-associated APP mutations induce alterations in the neurotransmitter transcriptomics of enteric neurons (147). APP itself can directly regulate the phenotype and function of intestinal macrophages, including cytokine secretion and microbial response (148). APP mutations associated with AD might alter the biology and behavior of intestinal macrophages. Thus, abnormal macrophage activation and neuronal activity may drive gut dysfunction and chronic inflammation, potentially aggravating CNS pathology through immune mediators or neural circuits. Targeting intestinal macrophages or the microbiota to reduce intestinal inflammation may ameliorate AD symptoms.

3.1.2. Parkinson's disease

PD is a progressive and debilitating ND characterized by motor function deficits due to the loss of dopaminergic neurons in the substantia nigra (SN) and the formation of intraneuronal protein inclusions called Lewy bodies, which are composed of misfolded α-synuclein (α-SYN) (149). As mentioned earlier, PD patients also experience GI disorders, with constipation being a typical symptom in the majority (150). Impaired GI motility can occur many years before a PD diagnosis, and intracellular Lewy bodies have also been found in enteric neurons (151, 152). This has led to the speculation that PD may originate from the gut. The simultaneous occurrence of increased gut inflammation and epithelial permeability suggests a fundamental role for immune cells and microbiota in the gut-related progression of PD (153-155). Intriguingly, there is evidence suggesting that PD can also initially develop in the brain (156-158). Nonetheless, regardless of whether the onset of PD in patients follows a brain-to-gut or gut-to-brain pattern, intestinal inflammation appears to be critical in promoting PD pathology through the GBA.

As observed in AD patients, gut dysbiosis and the associated inflammation are closely linked to the progression of PD. For instance, compared to healthy individuals, PD patients often show an altered gut microbiome, characterized by an increased abundance of *Enterobacteriaceae*, which positively correlates with the severity of certain PD symptoms, and decreased levels of anti-inflammatory bacteria such as *Prevotellaceae* (159, 160). *Enterobacteriaceae* are strongly associated with gut inflammation in patients with Crohn's disease, a type of IBD (161). Patients with Crohn's disease have an increased risk of developing PD, and notably, the use of anti-inflammatory drugs can partially reduce this risk (161). Gut inflammation could be a driving factor in the development of brain damage in PD patients. Mucosal macrophages play a key role in sustained intestinal inflammation through their interactions with luminal bacteria, although this aspect has been scarcely studied in the context of PD. Currently, there is limited research on the potential relationship between commensal bacterial strains and macrophage biology in the gut. In the blood of

PD patients, increased levels of cytokines such as TNFα, IFNγ, IL-1β, and IL-6, are associated with immune dysregulation in both the periphery and the brain (162). These cytokines could be largely secreted from intestinal macrophages. Microbial metabolites such as SCFA butyrate can promote cytokine secretion and enhance antimicrobial activity by inhibiting the mTOR pathway in macrophages (163). Moreover, microbe-derived LPS can strengthen the production of proinflammatory cytokines by intestinal macrophages. These cytokines can act directly on the BBB through the circulatory system, contributing to its destruction during PD progression (153). Remarkably, fecal microbiota transplantation (FMT) treatment has been shown to improve GI dysfunction and motor deficits in various PD mouse models (164, 165). It has been revealed that this improvement is related to the inhibition of the LPS-activated TLR4/MyD88/NF-κB pathway and its downstream proinflammatory products, such as TNFα, in myeloid cells of both the brain and the colon (164, 165). Furthermore, intestinal microbes synthesize neurotransmitters such as norepinephrine, GABA, serotonin, and dopamine, which can directly modulate macrophage function through neurotransmitter-receptor pathways (6, 25). Lewy bodies found in enteric neurons have been shown to spread to the brainstem via vagus sensory nerves (152). Investigating whether macrophages associated with neurons contribute to α-SYN pathology reaching the brain via neural pathways is worth pursuing. Overall, intestinal macrophages may contribute to PD progression through multiple pathways. Future efforts to manipulate beneficial gut bacteria or target inflammatory myeloid cell populations could provide novel therapeutic options for PD.

3.1.3. Huntington's disease

HD is an inherited ND caused by a CAG trinucleotide repeat expansion in the huntingtin *(HTT)* gene (166). Mutated huntingtin proteins misfold and accumulate as cellular inclusions in neurons, astrocytes, and microglia, leading to brain damage and atrophy (167). In addition to neurological symptoms such as motor and cognitive abnormalities, HD patients experience various GI disturbances, including reduced motility, diarrhea, and nutrient malabsorption (168).

Recent studies have found that gut dysbiosis is associated with HD pathogenesis and coincides with weight loss in both preclinical mouse models and HD patients (168-170). However, studies identifying the mechanisms by which gut microbiota contribute to HD progression remain scarce. The speculated mechanisms involve immune system dysregulation, defective autophagy and proteinopathies, neuroactive metabolites, neurotransmitter imbalances, and aberrant neural circuits (171-173). Increased intestinal epithelial permeability, described as "leaky gut," has been observed in R6/1 and R6/2 HD mouse models (168, 169). Macrophages are the main force responsible for maintaining barrier integrity (47, 82). However, it is presumed that in this context, mucosal macrophage activity tends to damage rather than repair the epithelial layer. In the plasma of HD patients, increased levels of proinflammatory cytokines such as TNFα, IL-6, IL-12, and IL-8, and anti-inflammatory cytokines including IL-4 and IL-10, are observed as the disease progresses (174, 175). Intestinal macrophages may play a significant role in local immunomodulatory imbalance and elevated levels of circulating cytokines. Furthermore, neuron-associated macrophages may crosstalk with vagal efferent nerve endings to modulate the release of anti-inflammatory mediators mediated by the cholinergic anti-inflammatory pathway (123). Neuron-associated macrophages may also contribute to the intraneuronal dissemination of mutant huntingtin proteins within enteric neurons (176). Thus, an in-depth exploration of macrophage-associated networks may reveal new pathogenic pathways and peripheral therapeutic targets for HD.

3.2. Neuropsychiatric disorders

Communication along the GBA also impacts neuropsychiatric disorders, such as depression, anxiety, and autism (5, 6, 177). In recent decades, the incidence of neuropsychiatric disorders has increased significantly, affecting a large number of people worldwide (178). Patients with psychiatric diseases experience compromised health and social activities. The etiopathogenesis of these disorders has been reported to be complex, involving factors such as genetic predisposition, injuries, infections, and environmental cues (179). Of note, studies in recent years have revealed that alterations in the GI system play an important role in the development of autism and mood disorders (5-7). Particularly, as the disease progresses, the gut symbiotic microbiota in patients alters, and intestinal inflammatory states strongly reflect these changes (180).

The gut microbiota shapes and instructs intestinal mucosal immunity throughout life. The interaction between commensal bacteria and intestinal macrophages affects both local immunity and distal immune activation, which are implicated in a range of psychiatric disorders such as depression (5). Gut dysbiosis leads to the accumulation of inflammatory myeloid cells and proinflammatory cytokines such as TNFα and IFNγ in the blood, which are positively correlated with depressive and anxiety-like symptoms (181, 182). Studies in both animals and humans have demonstrated that manipulating gut microbial composition influences the levels of inflammatory cytokines in the systemic circulation and the brain (183, 184). Under normal conditions, a delicate balance between the microbiota and the mucosal immune system ensures that only minimal levels of cytokines enter the bloodstream. Disturbances in microbial composition induced by antibiotics or probiotics can disrupt this balance, leading to altered cytokine profiles in monocyte and macrophage populations (184, 185). In patients with irritable bowel syndrome, administering the probiotic *lactobacillus* or *Bifidobacterium* alters the ratio of anti-inflammatory to proinflammatory cytokines released from peripheral blood monocytes, leading to an improvement in bowel symptoms (184, 185). Importantly, a study examined how chronic gut inflammation influences brain behavior (186). The results revealed that treatment with anti-inflammatory agents or the probiotic *Bifidobacterium longum*, but not vagotomy, can improve chronic GI inflammation-induced anxiety-like behavior in mice (186). These findings suggest that gut microbiota-brain interactions may primarily depend on circulating cytokines rather than the vagus nerve for regulating brain behavior.

GI dysfunction is very common in individuals with autism spectrum disorder (ASD) (187). ASD symptoms vary but are primarily characterized by changes in behavioral domains, including impaired social communication and restricted, repetitive patterns of behavior. A positive correlation between behavioral severity and GI symptoms has been observed (187), suggesting a link between the gut and brain neurodevelopment. Compared to their neurotypical counterparts, individuals with autism display altered gut permeability and increased susceptibility to intestinal inflammation (6). Furthermore, several studies have reported significant differences in the composition of gut microbiota between individuals with ASD and neurotypical individuals (188-190). An investigation has shown that gut dysbiosis contributes, at least in part, to the symptoms of autism by significantly increasing LPS levels in the bloodstream (191). The inflammasome pathway in macrophages can be activated through distinct PAMPs in response to microbes, leading to the production of active proinflammatory cytokines such as IL-18 and IL-1β (192). Patients with psychiatric disorders such as ASD have higher levels of IL-18, IL-1β, and TNFα in their blood compared to healthy controls (182). Increased levels of these cytokine likely cause damage to the BBB and subsequently affect CNS functions, including cognition, learning, and memory (193, 194). In the future, the intricate relationships between gut microbiota, intestinal inflammation, macrophage activity, and brain behaviors warrant further exploration.

3.3. Traumatic brain injury

Traumatic brain injury (TBI) represents a leading cause of morbidity and mortality in adults worldwide (195). Acute care management of TBI focuses on preventing and reducing primary neurological injuries and secondary sequelae effects on peripheral organs. TBI has been defined as a chronic and long-term disease that significantly impacts other organs, particularly the GI tract. The sequelae of TBI in gut tissues include mucosal barrier dysfunction and dysmotility (196). It has been proposed that following TBI, increased epithelial permeability triggers gut defenses, including immune cell activation, enteric neuronal and glial responses, and altered smooth muscle contractility (196). In addition, increased microbial infection exacerbates and prolongs intestinal inflammation, resulting in higher levels of circulating proinflammatory mediators. Studies have shown that during the post-TBI period, the GI tract is a major source of increased proinflammatory mediators in the circulatory system, playing a pivotal role in driving organ dysfunction by inducing long-lasting systemic inflammation (197, 198).

Systemic inflammation has been found to persist for months in patients suffering mild or severe TBI (199, 200). The populations of circulating $CD11b^{+}CD14^{+}$ monocytes and macrophages increase rapidly and substantially in patients following brain injury (201). Compared to age-matched healthy controls, TBI patients frequently show increased levels of both anti-inflammatory and proinflammatory cytokines, including IL-1β,

IL-6, IL-8, IL-10, and TNFα, in their blood (199, 202). Elevated levels of circulating cytokines and chemokines are associated with poor outcomes in patients with TBI (199). Large amounts of immune mediators in the circulatory system can have detrimental effects on both the CNS and peripheral organs, hindering overall recovery from TBI (203-205). Thus, it can be deduced that inflammatory responses originating from the impaired gut wall, involving the activation and reprogramming of intestinal immune cell populations, predominantly resident macrophages, promote CNS pathology via a systemic immune response (198, 206). Intestinal macrophages are known to release various proinflammatory mediators that reshape local adaptive immune responses and alter the activities of adjacent neurons and smooth muscle cells. Gut inflammation can sensitize visceral afferents, and proinflammatory macrophage activity may disrupt the cholinergic anti-inflammatory pathway by altering neurotransmitter synthesis in neighboring neurons (124, 127, 207). Alterations in blood monocyte differentiation may lead to the accumulation of proinflammatory monocytes and macrophages in the gut and bloodstream, thus exacerbating systemic inflammation. Moreover, increased levels of circulating microbial products and proinflammatory cytokines released from both enteric and systemic myeloid cells can accelerate the breakdown of the BBB. Enhanced access of circulating immune cells and mediators to the CNS, along with activated microglia, contributes to persistent neuroinflammation and progressive neurodegeneration following TBI (208, 209). Therefore, restoring gut homeostasis, especially the immune balance between gut microbiota and immune cells, appears to be critical for mitigating TBI-induced neuropathology and organ dysfunction. Currently, although there is a better understanding of gut-brain communication in driving neuroinflammation after brain injury, the precise cellular and molecular mechanisms contributing to chronic TBI progression require further investigation. New treatments for TBI patients that target dysbiosis, macrophage function, or circulating mediators hold great promise.

4. CONCLUSION

Enteric neuroimmunology is an emerging field with numerous exciting research directions. In recent years, the importance of neuro-immune interactions along the GBA and their impact on various CNS disorders have been widely recognized. Extensive research has confirmed that changes in the composition or function of the gut microbiota profoundly affect the pathology and progression of neurological disorders. The immune system serves as an important regulator, linking the microbiota, nervous systems, barrier structures, and behaviors through the GBA. Activation of immune cells in both the gut and the brain can lead to neuroinflammation or neurodegenerative diseases. Macrophages, the most abundant immune cell populations in the GI tract, play key roles in maintaining intestinal homeostasis and are essential for the development of many immune-mediated diseases affecting both the gut and the brain. Intestinal macrophages may influence the progression of CNS disorders by regulating the GBA, even though the specific molecular mechanisms involved are not yet fully understood. Recent advances in the study of intestinal macrophages have revealed their distinct functional specializations. Intestinal macrophage subpopulations in different anatomical niches exhibit distinct functions, making them multitaskers within the gut. Notably, intestinal macrophage subsets associated with neurons, smooth muscle cells, or blood vessels are linked to various GI pathophysiological conditions. However, the specific contribution of different intestinal macrophage populations to CNS diseases through the GBA requires further investigation. Nonetheless, the therapeutic potential of modulating these cells in gut-associated CNS disorders is promising and worthy of further investigation.

List of Abbreviations

ACh	acetylcholine
AD	Alzheimer's disease
AhR	Aryl hydrocarbon receptor
AIM2	absent in melanoma-2
ALRs	absent in melanoma-2 (AIM2)-like receptors
APP	amyloid precursor protein
ASD	autism spectrum disorder
ANS	autonomic nervous system
Aβ	amyloid β
α-SYN	α-synuclein
α7nAChR	α7 nicotinic acetylcholine receptor
BBB	blood-brain barrier
BMP2	bone morphogenetic protein 2
CLRs	C-type lectin receptors

CNS	central nervous system
CSF-1	colony-stimulating factor 1
DAMPs	damage-associated molecular patterns
DRG	dorsal root ganglia
ENS	enteric nervous system
FMT	fecal microbiota transplantation
GBA	gut-brain axis
GI	gastrointestinal
GABA	γ-aminobutyric acid
HD	Huntington's disease
HPA	hypothalamic-pituitary-adrenal
HSCs	hematopoietic stem cells
HTT	Huntingtin
IBD	Inflammatory bowel disease
ICCs	interstitial cells of Cajal
iNOS	inducible nitric oxide synthase
LPS	lipopolysaccharide
MMs	muscularis macrophages
NDs	neurodegenerative diseases
NLRs	nucleotide oligomerization domain (NOD)-like receptors
NOD	nucleotide oligomerization domain
PAMPs	Pathogen-associated molecular patterns
PD	Parkinson's disease
PGE2	prostaglandin E2
POI	postoperative ileus
PRRs	pattern recognition receptors
PSEN1	presenilin 1
RIG-I	retinoic acid-inducible gene-I
RLRs	retinoic acid-inducible gene-I (RIG-I)-like receptors
SCFAs	short-chain fatty acids
SN	substantia nigra
SPF	specific pathogen-free
TBI	Traumatic brain injury
TLRs	Toll-like receptors
Tregs	regulatory T cells
TRPV4	transient receptor potential vanilloid 4
VG	vagal ganglia

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Author contributions

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Conflicts of Interest

The authors declare no competing interests. ♦

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