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Review

Neuroinflammation in neurodegenerative disorders: Activation of microglia by microbial infection

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Abstract: Neurodegenerative disorders present a significant global health challenge. Neuroinflammation, which is a frequent occurrence of these diseases, may serve as an initial trigger. Emerging evidence suggests that microglia play a pivotal role as mediators of inflammation in the central nervous system. Disordered activation skews predominantly towards the M1 phenotype, which leads to neurotoxicity and neuroinflammation. Identifying the triggers of microglial activation is crucial to refine the therapeutic strategies for neurodegenerative diseases. Based on epidemiological, biological, and functional data, we observed a strong correlation between chronic microbial infection and microglial activation. This review outlines three potential inter-organ communication routes for infectious microbes in microglial activation—the gut-brain axis, the lung-brain axis, and the nose-brain axis— thus emphasizing the interaction between microglia and inflammation and proving that neuroinflammation is a significant factor in pathogen-induced neurodegenerative diseases. Collectively, we propose that therapies which target relevant inflammatory mediators, along with antibiotics that target neuropathogens, could potentially alleviate neuroinflammation and treat neurodegenerative diseases.

Keywords: neurodegenerative diseases; neuroinflammation; microbial infection; microglial activation; human microbiome

1. Introduction

Microglia, which are macrophages of the central nervous system (CNS), are pivotal for maintaining tissue homeostasis and eliminating pathogens and senescent cells. Recent research indicates that the pruning of synapses potentially contributes to neurodegenerative disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD). Neuroinflammation, a significant factor in numerous neurodegenerative diseases (NDs), is associated with all NDs and causes irreversible damage to CNS neurons. Inflammation not only fuels ND progression but also initiates it [1]. Upon neuronal injury or perturbation, microglia are activated, thus triggering local inflammation through proinflammatory factors and damaging adjacent healthy neural tissue. Defects in microglial maturation, differentiation, and function occur without complex microbiota, and microbial dysbiosis due to infection may trigger neuroinflammation and ND through microglial activation [1].

Hence, this article reviews and elucidates the interaction between microbiota and microglia in neurological disease development, thereby focusing on how neuroinflammation leads to NDs, how activated microglia induce neuroinflammation, and how microbiota activates microglia, thud leading to NDs via three pathways: the gut-brain axis, the lung-brain axis, and the olfactory-brain axis.

2. Neuroinflammation instigates neurodegenerative diseases

Endowed with microglial inflammation, numerous NDs, including AD, PD, HD, Amyotrophic Lateral Sclerosis (ALS), and Frontotemporal Dementia (FTD), may be instigated or exacerbated [2]. In the 1990s, significant epidemiological and observational studies indicated that anti-inflammatory treatments for conditions such as rheumatoid arthritis exhibited protective properties against AD, thereby reducing the risk of AD by 50 % in long-term Nonsteroidal Anti-inflammatory Drugs (NSAID) users. Chronic inflammation-related diseases such as diabetes, obesity, atherosclerosis, and depression potentially elevate the risk of neurodegeneration [2]. An upregulation of inflammatory markers (e.g., IL-6, IL-8, and TNFα) is evident in patients with NDs [3] (Table 1).

Table 1. Different pathways of neuroinflammation leading to neurodegenerative disorders.

Results	Medium	Effects	Ref
Synapse Reduction and Synaptic Dysfunction	Glutamate transporter	Excitotoxicity induced by elevated glutamate levels	[4]
	Nptx2	Neurotoxicity induced by complement activation	[4]
	CX3CL1	CX3CL1 promotes synaptic pruning by microglia	[5]
	calcium	Calcium accumulation promotes synaptic pruning	[6]
Neuronal Apoptosis	inflammatory mediator	\	[7]
	reactive oxygen	\	[7]
	TNF-TNFR1, RIPK1, caspase	Activation of complex IIa triggers caspase activation and leads to RIPK1-dependent apoptosis	[7]
		Complex IIb is formed, leading to necrosis	[7]
	Fas, caspase	Cleavage of molecular substrates induces neuronal apoptosis	[7]

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Results	Medium	Effects	Ref
tau Pathology	NLRP3, Tau kinases and phosphatases	Abnormal tau phosphorylation and aggregation result in synaptic loss	[8]
	inflammatory factor	Tau is phosphorylated or truncated	[9]
	N-glycosylation, O-GlcNAcylation	Tau is phosphorylated and aggravated	[10]
Further Activated microglia	Peripheral immune cells	Activated microglia shift to a proinflammatory phenotype	[11]
	proinflamatory cytokines	Proinflammatory cytokines activate microglia	[11]
	endoplasmic reticulum	Oxidative stress triggers an immune response	[11]
	Immunogenic molecules	Activated microglia and increased cytokine and ROS production	[11]
Amyloid protein misfolding and abnormal aggregation	microglia	Weakened clearance of Aβ plaque	[12]
	autophagy	Increased Aβ production	[12]
	NLRP3	Enhanced aggregation of amyloid	[12]
	ASC protein	It binds to Aβ and promotes its aggregation; NLRP3 is activated	[12]

2.1. Neuroinflammation elicits synapse reduction and impairment

Synapses, pivotal for information transmission, cause structural damage and dysfunction during neuroinflammation. This often precedes neuronal death in NDs. Neuroinflammation impairs astrocyte glutamate transporters, and an overexposure to extracellular glutamate results in synaptic damage. This is amplified by increased AMPA and NMDA receptors in the postsynaptic membrane and diminishes inhibitory synaptic transmission [4]. In a mouse model of neuroinflammation, diminished neuronal pentraxin expression can trigger neurotoxicity and neurodegeneration via complement activation, whereas Nptx2 overexpression is linked to A higher hippocampal synaptic density and reduced synaptic damage [4].

Microglia, which are key modulators of synaptic pruning through phagocytic sequestration, are influenced by inflammatory stimuli. Schizothoracin ligand, a G protein-coupled receptor-like chemokine, has been demonstrated in neurons to induce microglial synapse pruning via schizothoracin receptors and a dependency on neuronal activity [5]. Moreover, in neuroinflammatory models, microglia-constructed synapses correlate with local calcium accumulation [6].

2.2. Neuroinflammation stimulates neuronal apoptosis

In NDs, neuronal loss occurs via apoptosis, necrosis, iron/copper death, and neuroinflammation, which potentially mediates apoptosis. Apoptosis is activated via intrinsic (mitochondrial) and extrinsic (death receptor) pathways. Chronically elevated levels of proinflammatory molecules and reactive oxygen species (ROS) cause mitochondrial and DNA damage, thus initiating neuronal necrosis and enduring apoptosis. Extrinsic death receptors such as TNF-α and Fas ligands induce neuronal apoptosis during inflammation. TNF-α stimulates TNFR1 to form membrane-associated complex I via homotypic interactions with TNFR1 DD50, thereby assembling RIPK1 and TRADD. RIPK1 activation triggers caspase activation and apoptosis, and insufficient caspase activity results in necrosis

via the RIPK1-RIPK3-MLKL complex (complex IIb), and Fas activation via caspase cleavage substrates leads to apoptosis [7].

2.3. Neuroinflammation intensifies tau pathology

Tau pathology is a hallmark of multiple NDs, and distinct inflammatory mechanisms underlie its progression.

In AD, tau pathology and neuroinflammation form a pathological loop that accelerates the disease progression. A defining feature is how neuroinflammation directly drives tau hyperphosphorylation largely through the activation of the NLRP3 inflammasome. Using mouse models, Ising et al. demonstrated that the genetic deletion of NLRP3 significantly reduced tau aggregation, thus highlighting the central role of this inflammasome in tauopathy [8]. Beyond NLRP3, proinflammatory cytokines, such as IL-6 and TNF-α, amplify tau phosphorylation via the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway. For example, IL-6 binding to its receptor activates JAK kinases, which phosphorylate STAT proteins, translocate to the nucleus, and upregulate kinases (e.g., glycogen synthase kinase-3β, GSK-3β) that hyperphosphorylate tau [9]. This cascade not only promotes tau misfolding, but also impairs the microglial clearance of pathological tau, thus creating a self-sustaining cycle of inflammation and neurodegeneration.

While α-synuclein is the hallmark pathological protein in PD, tau pathology remains a critical underappreciated contributor, especially in the context of neuroinflammation. In the substantia nigra, neuroinflammation exacerbates tau misfolding via microglial activation. As shown by Wang et al. [18], α-synuclein oligomers released by damaged neurons bind to microglial pattern-recognition receptors (e.g., TLR2/TLR4), thus triggering a proinflammatory response. Activated microglia release IL-1β, which then activates GSK-3β in neurons [18]. This kinase phosphorylates tau at pathological sites (e.g., Ser396/404), thus promoting tau aggregation and spreading to connected brain regions. Notably, tau pathology in PD often overlaps with α-synuclein lesions, thus suggesting synergistic interactions. Neuroinflammation induced by α-synuclein accelerates tau misfolding, while tau aggregates further activate microglia, thus amplifying neurodegeneration in the midbrain and beyond.

FTD shows a unique interplay between neuroinflammation, tau pathology, and microglial phenotypes. A key mechanism involves inflammation-induced tau truncation at codon 217, which is driven by caspase-3 activation in neurons. Post-mortem studies of patients with FTD revealed that truncated tau (Δtau217) accumulates in regions with high microglial M1 polarization, which is characterized by proinflammatory cytokine release (e.g., IL-1β, TNF-α) and phagocytic dysfunction [10]. Caspase-3, which is activated by either oxidative stress or cytokine signaling, cleaves full-length tau at Asp216, thus generating Δtau217. These truncated tau species are more prone to aggregation and resistance to proteasomal degradation, thus forming neurotoxic fibrils that further activate microglia. Importantly, M1-polarized microglia perpetuate this cycle; their proinflammatory cytokines (e.g., TNF-α) upregulate neuronal caspase-3, which drives additional tau truncation. This pathway underscores how inflammation shapes tau pathology in FTD, thus linking microglial activation directly to neurotoxic tau transformations.

2.4. Neuroinflammation amplifies microglia activation

The neuroinflammatory response catalyzed by microglia escalates its activity, thus forming a self-

perpetuating cycle. This process involves immune cell invasion, proinflammatory cytokine release, microglial stimulation, and neural tissue damage. Research indicates that peripheral immune cell activation converts microglia into a proinflammatory state [11]. Elevated proinflammatory cytokines, including IL-1b, TNF-α, IL-6, and NOx, have been observed, with TNF-α being pivotal in the host defense system by stimulating microglia and causing progressive DAergic neuron loss in the substantia nigra (SN). TNF-α is upregulated in the SN of patients with PD, and its levels are elevated in the cerebrospinal fluid (CSF) of patients with PD. Chronic inflammation intensifies endoplasmic reticulum oxidative stress in microglia, thus triggering immune responses that are cell-dependent. Neuroinflammation fundamentally results from overwhelming immunogenic stimuli (such as pathogens or tissue damage). Under these conditions, immunogenic molecules can stimulate microglia to adopt amoeboid morphologies and significantly amplify cytokine and ROS production.

2.5. Neuroinflammation influences amyloid protein misfolding and abnormal aggregation

Common amyloid proteins include β-amyloid (Aβ) and α-synuclein (α-syn). Amyloid cascade hypotheses, the current primary models explaining AD pathogenesis, propose that Aβ misfolding and aggregation triggers a linear cascade which leads to AD pathology. The abnormal aggregation of α-syn, which is seen in Lewy bodies (LB) and Lewy neurons, is associated with various sporadic NDs and is termed alpha-synucleinopathy. Inflammation potentially impacts the progression of AD by promoting amyloid protein misfolding and abnormal aggregation and impairs microglial function, which reduces their ability to clear Aβ plaques and leads to Aβ accumulation. Additionally, it can stimulate increased Aβ production via the activation of autophagy in the nervous system. Defects in autophagy impair Aβ secretion, and the amyloid precursor protein (APP) and the γ-secretase complex are located in the autophagosome, thus suggesting a link between Aβ peptide production and the autophagy pathway. Alternatively, neuroinflammation may induce NDs by activating the NLRP3 inflammasome through enhanced amyloid aggregation. NLRP3 inflammasome activity is notably increased in NDs. Inflammation leads to increased ASC protein expression in neutrophils, and ASC plaques can bind Aβ and promote aggregation; inflammasome suppression increases the α-syn oligomer degradation rate. Additionally, the amyloid protein binding to ASCs may activate NLRP3, thus accelerating disease progression and causing neurotoxicity [12].

3. Activated microglia exacerbate neurodegeneration via inflammation

Microglia, which are crucial CNS immune cells, swiftly respond to antigens and become prone to inflammation with age. Age-associated dysregulation makes them susceptible to immune challenges, thereby augmenting Aβ pathology, impairing TGF-β signaling, and significantly suppressing purinoceptors [12]. This deficiency in neuron-derived immune regulators, such as the CX3CL1 ligand, fuels microglial hyperactivity [13]. Chronically stimulated microglia induce neuroinflammatory responses through diverse pathways. The triggered cells were either designated M1 or M2: M1 microglia are detrimental, discharging proinflammatory cytokines, chemokines, and ROS; conversely, M2 microglia are restorative, generating anti-inflammatory cytokines [14]. The augmentation of Hv1/NADPH oxidase in the aging brain biases microglial activation towards M1 polarization, thus amplifying neuroinflammation. Nonetheless, the M1/M2 classification scheme has been refuted and replaced with a state-based model (Figure 1).

Figure 1 shows the mechanism underlying neuroinflammation instigated by senescent microglia. TREM2 receptor deficiency combined with the compromised phagocytosis of apoptotic neurons by microglia triggers neuronal β-amyloid aggregation. This aggregation sparks extracellular deposition, which stimulates the synthesis and secretion of proinflammatory cytokines (such as TNF-α, IL-1β, and IL-6). Simultaneously, TNF-α binding to TNFR on microglial surfaces initiates the NF-κB pathway, thus amplifying the release of proinflammatory factors. Senescent microglia exhibit diminished phagocytic pouches and elevated anti-phagocytic receptor CD22 levels, thus reducing their phagocytic potential. Moreover, lipopolysaccharides (LPS), a TLR4 ligand in these cells, promotes lipid droplet formation, which not only hinders phagocytosis but also elevates the expression of genes related to nitric oxide and ROS production (e.g., CAT, KL, PPP1CB, JAK, and RAP1B), thereby promoting NOX2, MPO, and iNOS production and enhancing ROS and nitric oxide (NO) release. ROS interacts with pattern recognition receptors (PRRs) to stimulate NLRP3 inflammatory vesicles within the endoplasmic reticulum, thus leading to the enhanced synthesis and secretion of proinflammatory cytokines such as IL-1β. Additionally, augmented mtRNA levels in senescent microglia trigger cGAS-STING signaling, thus augmenting cytokine release. These proinflammatory factors induce α-synuclein aggregation in neurons, which subsequently interacts with RAGE, thus initiating downstream signaling pathways that amplify inflammation and complete a positive feedback loop.

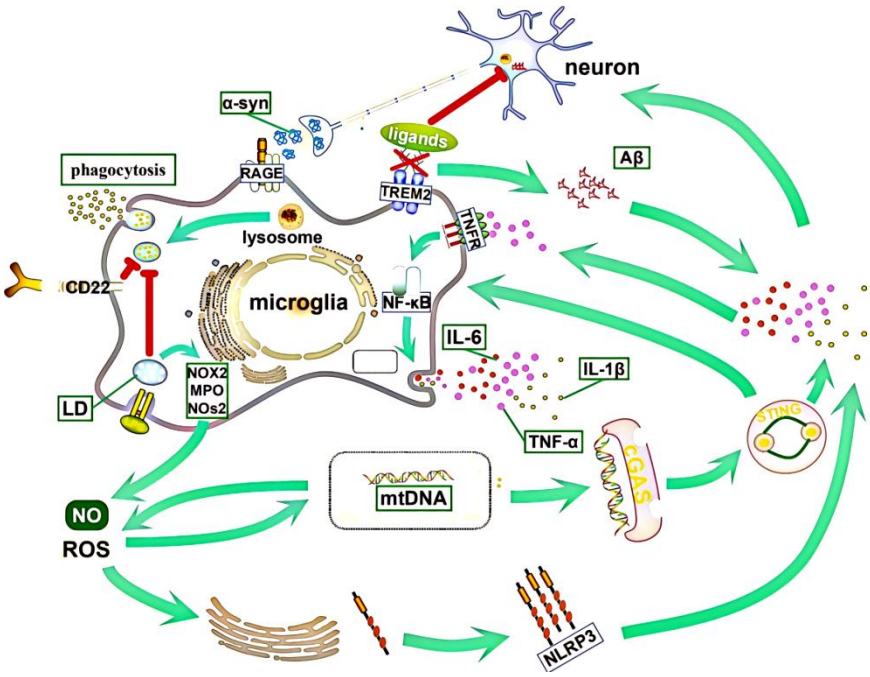

Figure 1. Mechanism underlying neuroinflammation instigated by senescent microglia.

3.1. Activated microglia generate increased inflammatory factors

Aged microglia secrete elevated levels of proinflammatory cytokines such as TNF-α, IL-1β, and IL-6. This may be associated with NF-κB activation. These cytokines are also increased in aged rodent brains. Chronic activation of aged microglia has also been observed. Evidence indicates that LPS-induced lipid droplet formation and accumulation in aged microglia correlates with

increased basal production of inflammatory cytokines and exaggerated cytokine release post-immune challenge [15,16]. Furthermore, increased mtRNA abundance in aged microglia stimulates cGAS-STING signaling, this leading to innate immune activation in the aging brain. This results in the elevated expression of inflammatory and interferon-associated genes, thereby amplifying proinflammatory cytokine secretion [17]. Proinflammatory factors induce α-synuclein aggregation in neurons, which potentially propagate neurodegeneration through cell-to-cell transmission. In turn, α-synuclein reactivates microglia, further stimulating cytokine release [18].

3.2. Decreased phagocytosis in activated microglia promotes neuroinflammation

Phagocytosis by microglia, which is essential for apoptotic cell removal and myelin debris clearance, supports tissue repair and influences oligodendrocyte progenitor cell maturation. Enhancing this process mitigates inflammation and positively correlates with favorable neuroinflammatory outcomes. Additionally, microglia efficiently sequester Aβ and inhibit cytokine synthesis [19]. Microglia possess specialized phagocytic pouch membranes, which are crucial for adult hippocampal neurogenesis. Reduced numbers of these pouches in older individuals indicate diminished microglia phagocytosis [20]. Aged mice have shown decreased TREM2 expression in microglia, thus potentially impairing neuronal phagocytosis and promoting protein aggregation. Furthermore, the anti-phagocytic receptor CD22 was upregulated in aging microglia, thus enhancing debris and protein aggregate phagocytosis using a specific blocking antibody.

3.3. Increased emission of reactive compounds promotes neuroinflammation

Microglia primarily generate ROS and NO in the CNS. Excessive ROS production induces oxidative stress owing to the diminished antioxidant capacity [21]. In NDs, oxidative stress corresponds to immune activity, which suggests that ROS engages with PRRs to stimulate the NLRP3 inflammasome, thus launching innate immunity. This process escalates proinflammatory cytokine production, thereby catalyzing pyroptosis and innate immune responses [21]. Activated microglia elevate ROS and NO release via the induction/stimulation of NOX2, MPO, and iNOS, also known as Nos2. Senescent microglia exhibit heightened activation, with TNF-α stimulating elevated iNOS2 and proinflammatory factor expression, amplifying NO and ROS release, and intensifying neuroinflammation. The accumulation of lipid droplets in senescent microglia and the upregulation of genes linked to NO and ROS production in high-lipid-droplet microglia have also been observed [15].

The ROS-NLRP3 inflammasome pathway and the LPS-TLR4-NF-κB signaling pathway play crucial roles in the pathological processes of neuroinflammation and neurodegenerative diseases. In the ROS-NLRP3 inflammasome pathway, ROS generated by NOX2/MAPO systems in microglia are key triggering factors. The accumulation of ROS disrupts the intracellular ion balance and induces potassium efflux. This ionic imbalance serves as an important signal to initiate the activation of the NLRP3 inflammasome, thus prompting the oligomerization of the NLRP3 protein, which then binds with apoptosis-associated speck-like protein containing a CARD (ASC) to form a complex. The formation of this complex subsequently activates caspase-1, which cleaves inactive precursors of IL-1β and IL-18 and converts them into their biologically active mature forms, which are then secreted extracellularly, thereby triggering an inflammatory response [22]. Notably, during the pathological process of AD, the presence of Aβ plaques further exacerbates the inflammatory response. Research

by Jafari et al. [6] showed that Aβ plaques can enhance the release of mitochondrial ROS, leading to a further increase in the intracellular ROS levels. This promotes the overactivation of the NLRP3 inflammasome, intensifies neuroinflammation, and accelerates neuronal damage and death.

On the other hand, the LPS-TLR4-NF-κB signaling pathway uses LPS as the main activator. LPS can cross into the CNS via the blood brain barrier (BBB). Once inside, LPS specifically binds to the TLR4/MD-2 complex on the microglial surface. This binding event recruits myeloid differentiation primary response 88 (MyD88). Then, the recruitment of MyD88 activates the tumor necrosis factor receptor-associated factor 6 (TRAF6), which phosphorylates IκBα. Phosphorylated IκBα dissociates from the NF-κB complex to release NF-κB, which undergoes nuclear translocation, enters the nucleus, and binds to specific DNA sequences, thus inducing the expression of a series of proinflammatory genes, including TNF-α and IL-6[23]. Additionally, it triggers a type I interferon response, thus inducing the expression of genes, such as Mx1 and Irf7 [24,25]. The massive production of proinflammatory factors and interferons exacerbates neuroinflammation, disrupts the microenvironment of nerve cells, and plays a catalytic role in the occurrence and development of neuroinflammatory and NDs.

4. Microbes trigger microglia activation

As previously noted, the primary duty of microglia is to proficiently discern and phagocytose protein aggregates and cellular fragments without harming neighboring tissues to maintain CNS integrity [26]. Interestingly, overactive microglia induce neuroinflammation and thus play a vital role in NDs through various mechanisms [27]. The developmental, homeostatic, and pathogenic programs of microglia are guided by environmental factors and mechanisms, which remain elusive. In the CNS, microglial activity is regulated by cytokines, chemokines, neurotransmitters, and other molecules that control the signaling pathways that influence various brain functions. The BBB, once believed to insulate microglia from the circulatory system, has been refuted by recent studies. Recent research has highlighted microbiota-microglia interactions as a pivotal mechanism of microbiota-immunity-brain interactions [28]. A mutual symbiotic relationship has emerged because of the co-evolution of bacteria and the human host. In both homeostasis and disease, microbiota heavily rely on the host for nutrition and an ideal environment [29]. Notably, evidence suggests that an altered microbiome may instigate neuroinflammation by modulating microglial function and activation, with studies focusing on the gut, lung, and nasal microbiomes emerging as new territories [30]. Thus, we have amalgamated several pertinent prospective studies to illustrate the potential effects of microbiota on microglia via three possible routes from the site of infection to the brain: the gut-brain axis, the lung-brain axis, and the olfactory-brain axis (Figure 2).

Figure 2 shows how the gut microbiota, lung microbiota, and nasal microbiota may affect microglia through multiple pathways. Regarding the gut-brain axis, the gut microbiome regulates microglia maturation and activation by releasing metabolites, such as SCFA and neurotransmitters, alongside dysbiosis of the gut flora. Regarding the lung-brain axis, LPS released by the lung microbiota can cross the BBB to activate microglia to produce inflammatory mediators such as type I interferons; microbes or microbial products can directly invade neurons, further accelerating the neuroinflammatory response, which is consistent with the activation of microglia. Regarding the nose-brain axis, the relationship between alterations in the nasal microbiome and microglia activation is unclear, but the nasal microbiota triggers an inflammatory response that may be associated with an

abnormal activation of microglia; nasal microbiota may lead to inflammation by either affecting olfactory neurons or by activating local immune responses, as well as metabolites, and an abnormal activation of microglia leads to neurological inflammation, thus the nasal microbiota may be activated by microglia and lead to neurological inflammation.

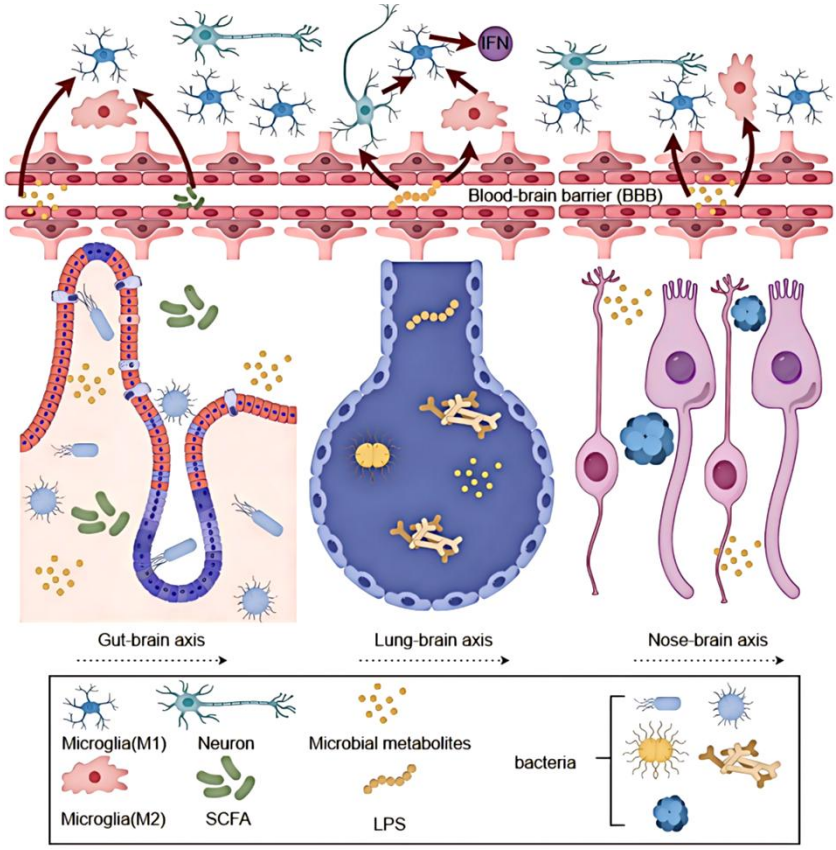

Figure 2. The gut microbiota, lung microbiota, and nasal microbiota may affect microglia through multiple pathways.

4.1. Gut-brain axis

The human gut microbiota, home to a diverse microbial population, contains approximately 150 times more genes than the human genome [31,32]. It plays a pivotal role in human growth and development, including diseases, aging, and health maintenance [33]. Recent research has indicated that a diverse gut microbiome is necessary for healthy microglial development and function [34]. Notably, specific strains such as Bifidobacterium longum modulate the microglial phenotype via GABA secretion, while Enterococcus faecalis-derived isoamylamine induces microglial apoptosis in aging models [44,46]. Throughout the host's lifespan, the gut microbiota provides critical trophic cues to microglia, thus shaping their phenotype in both health and disease [35–38]. Short-chain fatty acids (SCFAs), microbial metabolites produced by commensal bacteria, orchestrate microglial maturation and activation under homeostatic conditions [39,40]. *Lactobacillus paracasei* L9 affects disease progression in experimental autoimmune neuritis (EAN) by regulating the intestinal flora structure and arginine metabolism [41].

Notably, disruptions in the gut microbiota, such as those observed in germ-free animals or antibiotic-treated mice, lead to aberrant microglial phenotypes, including increased cell numbers, maturation defects, and morphological alterations (e.g., elongated protrusions, hyperbranching, and frosted synaptic processes) [42]. Quantitatively, germ-free mice exhibit a 40% reduction in microglial phagocytic pouches and a 60% decrease in TREM2 expression compared to specific pathogen-free controls, thus underscoring the role of microbiota in microglial functional priming [42]. Consistent with these findings, a post-mortem analysis of human AD brains revealed a 35% decline in $TREM2^{+}$ microglia, thus linking microbiota-driven microglial dysfunction to a neurodegenerative pathology [43].

Additionally, the gut microbiota modulates microglial immune surveillance against CNS insults, as microbiota-depleted mice show blunted responses to immunostimulants, such as LPS and lymphocytic choriomeningitis virus (LCMV), due to immature gene expression profiles [37,44]. Mechanistically, microbial-derived neurotransmitters, such as serotonin (produced by Enterococcus and Streptococcus), GABA (Bifidobacterium and Lactobacillus), and acetylcholine (Lactobacillus), influence microglial activation via direct receptor engagement and metabolic reprogramming [45,46].

Clinical evidence from Teng et al. demonstrated that *Enterococcus faecalis*-derived isoamylamine (IAA), a metabolite that crosses the BBB, triggers microglial apoptosis in aged mice through S100A8 signaling. This mechanism correlates with cognitive decline in humans, thus establishing a causal link between gut microbial metabolism and age-related neurodegeneration [47]. Collectively, these findings highlight the dynamic sensitivity of adult microglia to gut microbial shifts, thus emphasizing the need for continuous microbiota input to maintain neuroimmune homeostasis [37].

4.2. Lung-brain axis

The lung-brain axis works through intricate biological pathways. The respiratory tract, divided into upper and lower segments, serves as a primary interface for respiratory microorganisms, including bacteria, viruses, and fungi, which colonize the alveolar region of the lower tract [48]. Alterations in the lung microbiome have been linked to early-stage rheumatoid arthritis (RA) and disease progression [49], and emerging evidence has connected AD neuropathology to lung bacterial species. For instance, Bordetella pertussis infection induces Aβ deposition and neuroinflammation in mouse models [50], and clinical correlations exist between lung-brain axis dysfunction and comorbidities, such as cancer, in ASD patients [51]. This bidirectional axis is mediated by inflammatory and neuroendocrine pathways, such as brain cancer, ASD, acute respiratory distress syndrome, and neurologic dysfunction [52], with microglia acting as central regulators of lung microbiome-driven neuroinflammation.

Hosang et al. demonstrated that neomycin-induced lung microbiota dysbiosis exacerbates microglial M1 polarization in experimental allergic encephalomyelitis (EAE), yielding a 2.8-fold increase in IL-6+ microglia [53]. Concomitantly, bacterial LPS traverses the BBB via TLR4-dependent transcytosis, thus activating the MyD88/NF-κB signaling axis to upregulate the microglial Mx1, Mx2, Rsad2, Oas1a, and Irf7 genes [54,55]. Azzoni and Marsland elucidated that LPS engagement with TLR4 triggers endocytic transport across brain endothelial cells, thus culminating in NF-κB-mediated transcription of type I interferon (IFN) response genes, which paradoxically exert neuroprotective effects [55].

Microbial translocation across the 1-mm alveolar-capillary barrier further escalates neuroinflammation, with bacterial products invading neuronal synapses via axonal transport or the bloodstream. This process correlates with the increased expression of proinflammatory cytokines (IL-6 and IL-1β) and microglial activation [56,57]. Respiratory Syncytial Virus (RSV) infection exemplifies this crosstalk; viral-induced lung dysbiosis elevates α-estradiol secretion via the hypothalamic-pituitary-adrenal (HPA) axis, while oxidative stress and Th1-type immunity polarize microglia to a proinflammatory M1 phenotype in response to IL-1β, IL-6, IFN-γ, and microbial debris [58,59]. These findings underscore the lung-brain axis as a critical mediator of microglia-driven neuroinflammation in NDs.

4.3. Olfactory-brain axis

Numerous microorganisms reside within the human nasal cavity, including bacteria, viruses, fungi, and archaea, and owing to their unique positioning, nose microbiota signals reach the brain via the olfactory system. This bidirectional interaction influences neurological disorders including AD, PD, and multiple sclerosis.

Alterations in the nasal microbiota may precipitate early PD symptoms, including the loss of smell. Certain microbes, such as *Bifidobacterium bifidum*, can infiltrate the CNS and affect neurons through their interaction with nerve growth factors. This imbalanced microbiome may induce synaptogenesis aggregation and neurodegenerative progression originating from the anterior olfactory nucleus and spreading to regions such as the striatum and SN via cranial nerves from the peripheral nervous system (PNS) and other vulnerable areas of the CNS, potentially involving specific inflammatory responses.

The relationship between disturbed nasal microbiome and microglial activation is yet undefined; nevertheless, the microbiota triggers an inflammatory response potentially linked to deregulated microglial activation. The microbiota significantly mediates immune system functions, affects mucosal immunity, and contributes to localized inflammation. *S. aureus* infiltrates the olfactory epithelium, travels via axons to the olfactory bulb, and binds TLR2/6 on microglia, thus triggering the MyD88-dependent activation of MAPK and NF-κB, which releases proinflammatory factors (e.g., IL-1β, NO) [60]. The microbiota may infiltrate the brain by either affecting olfactory neurons or stimulating local immune responses such as mitochondrial damage, oxidative stress, and inflammation, which are associated with microglial activation [61]. Moreover, microbiota can manage inflammation via mechanisms such as tryptophan utilization and microbial metabolites of IFN-β, which restrain inflammation after IFN-β treatment in the nose [62]; this suggests that disrupted nasal microbiota might incite central neuroinflammation and that disordered microglial activation can trigger neuroinflammation, and that the nasal microbiota may stimulate microglia and thereby contribute to neuroinflammation. Germ-free animals exhibit reduced microglial numbers in the olfactory bulb, thus emphasizing the microbiota's role in maintaining microglial immunosurveillance [63]. Additionally, nasal microbial metabolites (e.g., tryptophan derivatives) modulate microglial inflammation via the aryl hydrocarbon receptor (AhR), thus linking mucosal immunity to central neuroinflammation [57] (Figure 3).

Figure 3 shows the gut-brain, lung-brain, and olfactory-brain axes, which represent critical pathways through which peripheral systems interact with the CNS. In the gut-brain axis, SCFAs act through receptors to HDACs, characterized by increased IL-10 and decreased TNF-α. Concurrently,

LPS from gut microbiota engage TLR4/MD-2 receptors on immune cells, thus triggering a MyD88-dependent pathway, which leads to the upregulation of proinflammatory genes encoding IL-1β and IL-6. In the lung-brain axis, LPS derived from lung microbiota activates TLR4/MD-2 receptors on bronchial epithelial cells (BECs), which initiates a MyD88-TRAF6 signaling cascade and results in releasing NF-κB to induce the expression of antiviral genes such as Mx1 and Irf7 and the elevation of proinflammatory cytokines IL-6 and TNF-α. The olfactory-brain axis involves the *Staphylococcus aureus*-mediated activation of TLR2/6 receptors on microglia. This leads to the production of proinflammatory mediators including IL-1β, NO, and ROS.

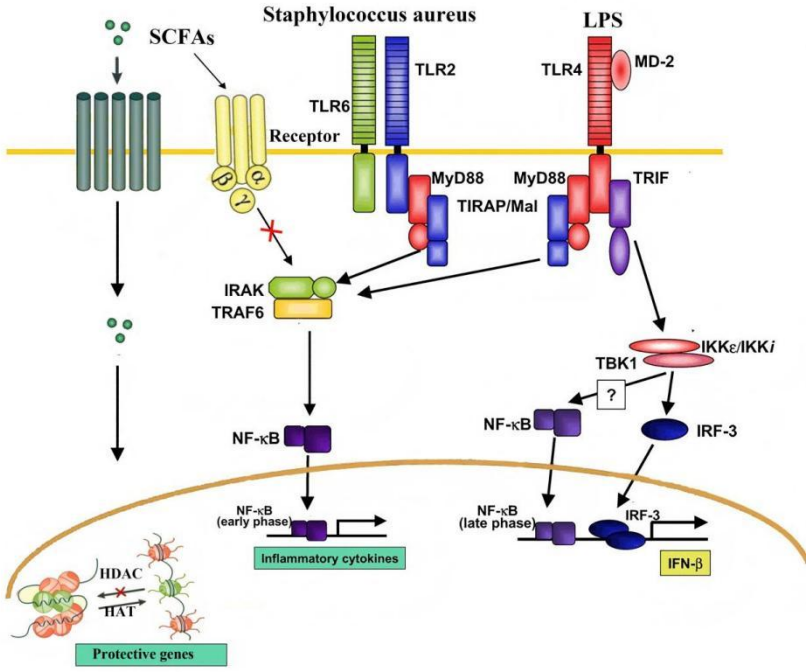

Figure 3. The gut-brain, lung-brain, and olfactory-brain axes represent critical pathways through which peripheral systems interact with CNS.

5. Discussion

Mounting evidence indicates that inflammation fuels ND progression and serves as the primary trigger [64]. For instance, inflammation substantially precedes protein aggregation, and persistently active STING expression instigates PD pathologies in mouse models [65]. However, clinical trials that employed anti-inflammatory treatments failed to decelerate disease progression, thus potentially reflecting the intricate role of inflammatory signaling in NDs [66]. As previously discussed, we have separately elucidated the cellular and molecular mechanisms of inflammation in NDs and the interplay between neuroinflammation and microglial activation to better understand their causal relationship in disease progression. Notably, neuroinflammation plays a dual role in disease development, where detrimental inflammatory signals in one stage may prove beneficial in the other. Additionally, proinflammatory responses are essential for the effective resolution of inflammation [67]. Consequently, we reviewed and integrated the signaling pathways between microglia and inflammation. We believe that future research and clinical trials are necessary to fully exploit the

potential of the immune system in understanding ND progression [68].

Numerous recent epidemiological studies have established a direct link between chronic microbial infections and neuroinflammation [69]. Given the biological intricacy of multi-cell and multi-organ interactions during microbial infections, we concentrate on describing infections that lead to neuroinflammation via microglial activation, thereby highlighting three inter-organ communication routes: the naso-brain, lung-brain, and gut-brain axes. Current research on the nasal microbiota-microglia axis in NDs has notable limitations. For instance, most clinical studies that investigated microbiota in patients with PD and AD enrolled fewer than 100 participants, thus significantly compromising the statistical power to detect meaningful associations. Technologically, 16S rRNA sequencing, the predominant method for a microbiota analysis, suffers from inherent limitations, as it fails to capture viral and fungal components of the microbiome, while comprehensive metagenomic sequencing remains prohibitively expensive for large-scale studies. Mechanistically, there is a critical knowledge gap: fewer than 3% of published studies have explored how microbes interact with microglial signaling pathways, with only isolated reports (e.g., Staphylococcus aureus-induced TLR2 activation) beginning to address this void [70].

To advance this field, future research should prioritize multi-omics approaches. Integrating metagenomic profiling with single-cell RNA-seq could map the transcriptional states of microglia in response to nasal microbial cues, as recently proposed by Loh et al. [30], to study the microbiota-gut-brain axis in AD. Additionally, precision intervention models, such as fecal microbiota transplantation in APP/PS1 transgenic mice, hold promise to dissect the causal relationships between nasal microbiota dysbiosis and microglial dysfunction (NCT04581068). These strategies are essential to bridge the translational gap and uncover actionable targets for neuroinflammatory diseases.

6. Therapeutic progress and challenges

Ongoing clinical trials in the fields of neuroinflammation and microglia-targeted therapies have shown promising results. For instance, the NLRP3 inflammasome inhibitor MCC950 has been shown to reduce brain IL-1β levels in phase 2 trials for AD (NCT03179705), thus highlighting its potential to mitigate the neuroinflammatory pathways central to AD pathogenesis. Concurrently, TREM2 agonists, such as AM001, have exhibited enhanced Aβ phagocytosis in preclinical models and entered phase 1 clinical trials in 2024, with the aim of leveraging microglial clearance functions for disease modification.

Microbiota-based therapeutic strategies are gaining traction. Fecal microbiota transplantation (FMT) in PD has shown promise in reducing intestinal permeability and decreasing microglial M1 polarization markers, as evidenced by a 22% reduction in $CD11b^+$ cells (NCT04581068), thus suggesting a potential avenue to modulate neuroinflammation via gut-brain axis regulation. Additionally, SCFA supplementation, particularly butyrate, has been shown in preclinical studies to restore microglial mitochondrial function in aged mice, which led to a 40% reduction in ROS production [34], underscoring the metabolic influence of microbial metabolites on microglial phenotype.

Despite these advances, several significant challenges persist. The BBB remains a formidable obstacle, with less than 3% of anti-inflammatory drugs achieving sufficient CNS penetration to exert therapeutic effects [71]. Moreover, microglial heterogeneity presents a complex targeting dilemma, as AD is associated with over 12 distinct microglial subsets, including disease-associated microglia

(DAMs), each requiring subtype-specific intervention strategies to selectively modulate harmful proinflammatory states while preserving beneficial homeostatic functions [72].

In conclusion, we suggest that microglia-induced neuroinflammation can elucidate potential microbial infection-mediated ND mechanisms, and that preventing microbial infections is a feasible intervention to manage microglial hyperactivity. To achieve this goal, more thorough experimental and clinical studies are required.

Author contributions

TJ, KZ, GK assembled references and drafted the document. GW and YT participated in discussions. GW and YT reviewed and refined the paper. All authors endorsed the final version.

Use of Generative-AI tools declaration

The authors declare they have used Artificial Intelligence (AI) tools in the creation of this article.

Conflict of interest

All authors declare no conflicts of interest in this paper.

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