

# Exploring the Connectivity of Neurodegenerative Diseases: Microglia as the Center

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**Abstract:** Degenerative diseases affect people's life and health and cause a severe social burden. Relevant mechanisms of microglia have been studied, aiming to control and reduce degenerative disease occurrence effectively. This review discussed the specific mechanisms underlying microglia in neurodegenerative diseases, age-related hearing loss, Alzheimer's disease, Parkinson's disease, and peripheral nervous system (PNS) degenerative diseases. It also reviewed the studies of microglia inhibitors (PLX3397/PLX5622) and activators (lipopolysaccharide), and suggested that reducing microglia can effectively curb the genesis and progression of degenerative diseases. Finally, microglial cells' anti-inflammatory and pro-inflammatory dual role was considered the critical communication point in central and peripheral degenerative diseases. Although it is difficult to describe the complex morphological structure of microglia in a unified manner, this does not prevent them from being a target for future treatment of neurodegenerative diseases.

**Keywords:** microglia, neurodegenerative diseases, neuroinflammation

## Introduction

Ageing is a risk factor for neurodegenerative diseases. The aging process contributes to the development of various degenerative diseases characterized by significant impairment in tissue or cellular functional disease.<sup>1</sup> Degenerative disease is a series of diseases caused by organ and tissue aging. Most chronic degenerative human diseases are inherently associated with increasing age.<sup>2</sup> The most common degenerative diseases are neurodegenerative disorders, such as age-related hearing loss (ARHL), Alzheimer's disease (AD), Parkinson's disease (PD), retinal degenerative diseases, etc.<sup>3-5</sup> The hallmark of these changes is the morphological alterations observed in nerve cells due to aging and other detrimental factors, including inflammation and cancer. Ultimately, these changes impact nerve function by leading to neuronal degeneration.<sup>6</sup> Some degenerative diseases are peripheral neurodegenerative diseases, such as pain neuron degeneration and osteoarthritis.<sup>7,8</sup> Although many studies are conducted on degenerative diseases, few study has explored the underlying commonality of these degenerative diseases. Therefore, exploring the commonality of central and peripheral mechanisms is vital in finding novel treatments, which is the objective of this review.

Over time, the theory of microglia as the main target of degenerative diseases has been suggested. Microglial cells have unique mechanisms, appearing as star cells in a hot circle. The first point to consider is that microglia are macrophages that reside in the brain and play a significant role in immunomodulation.<sup>9</sup> They are activated in response to various damaging factors such as aging, tissue damage, abnormal stimulation, neurotoxins, infection, etc. Moreover, they exhibit prompt responsiveness toward biological damage.<sup>10</sup> Second, unlike most immune cells, such as white blood cells, microglial cells, although their early response is protective,<sup>11,12</sup> can rapidly transform into pro-inflammatory cells

and initiate a series of neuroinflammatory responses, in which case they can physically attack healthy neurons through phagocytosis or the secretion of marcelling inflammatory cytokines.<sup>13</sup> This neuroinflammatory phenomenon is commonly seen throughout the disease course. With time, regulating pro- and anti-inflammatory signals has dynamic changes, such as converting the M1 phenotype with pro-inflammatory activity into the M2 phenotype with anti-inflammatory activity.<sup>14</sup>

The dual role of microglia in neurodegenerative diseases involves both pro-inflammatory and anti-inflammatory mechanisms. For instance, in Alzheimer's disease (AD), microglia can phagocytose A $\beta$  fragments to exert a protective effect; however, when phagocytosis is activated, it can lead to a pro-inflammatory response.<sup>15</sup> M1/M2 microglia can exhibit dual effects in peripheral degenerative diseases by releasing exosomes with distinct properties.<sup>16,17</sup> Additionally, the microglia-astroglia-gial axis serves as a potential avenue for information transmission between glial cells, allowing this dual effect to occur. Our research primarily investigates how this interaction can be harnessed to suppress the chronic activation of microglia. Thus, this positive feedback circulatory process leads to degenerative diseases. Therefore, inhibiting the chronic activation of microglia to prevent pro-inflammatory mediator production and synaptic phagocytosis can efficiently reduce neurodegenerative disease development.

The function of microglia is complex, and the morphology of various states is different, so it is difficult to put together a discussion. Therefore, to understand the function of microglia in the context of disease, it is important to understand their neuroinflammatory connectedness. We will discuss several examples of microglia function in the context of neuroinflammation, including central and peripheral diseases.(Figure 1).

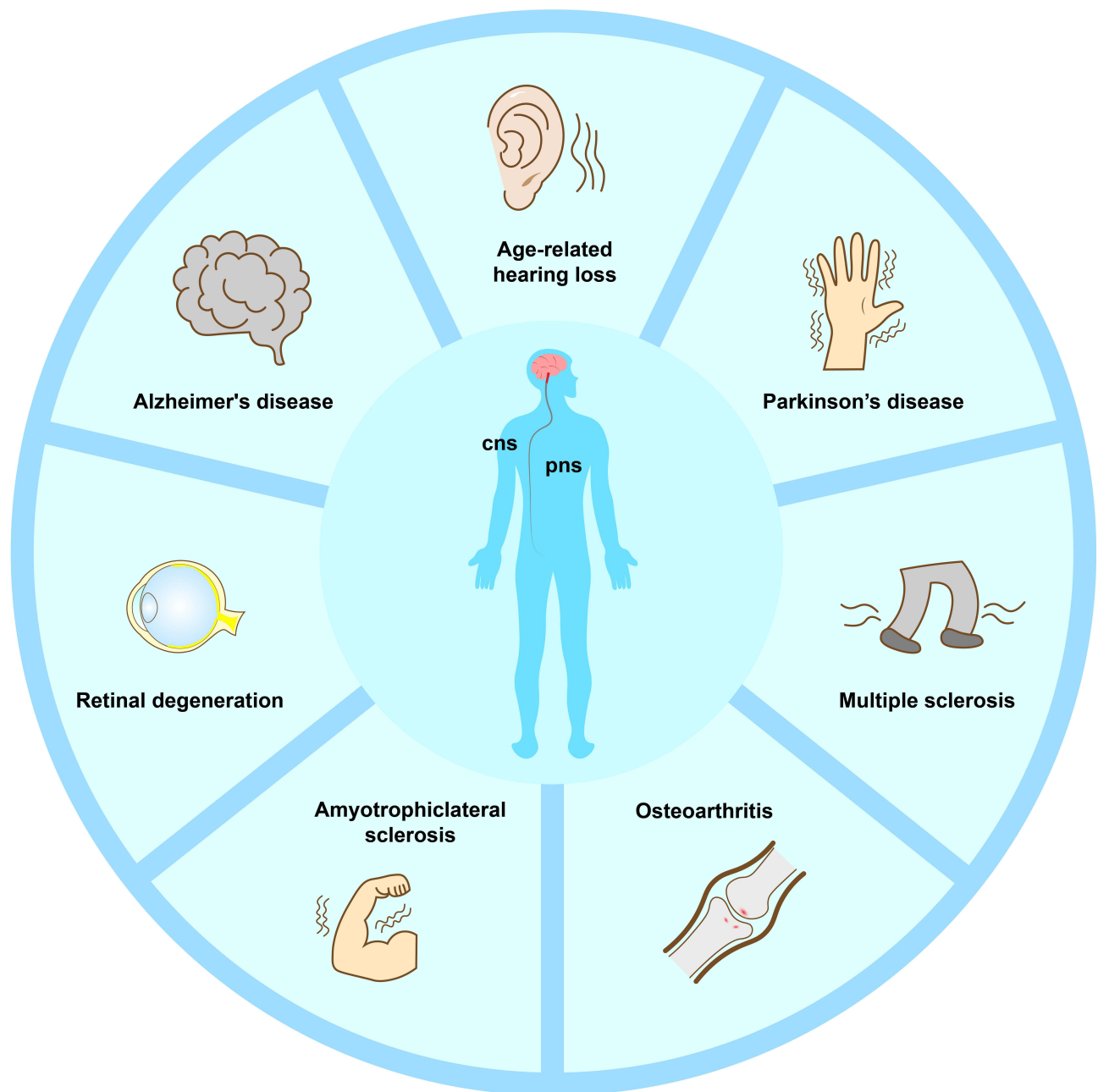
## Microglia and Neurodegenerative Disorders

### Microglia and Age-Related Hearing Loss

Age-Related Hearing Loss (ARHL) or presbycusis represents a frequently seen sensory impairment among older adults. With cochlear aging (peripheral hearing organ), hearing loss may develop and is associated with increased sensory nerve cell degeneration risk in the cochlea and worsening of age-related hearing loss, which seriously affects patient's quality of life. Considering the serious aging problem worldwide and the social burden due to ARHL,<sup>18</sup> treatments alleviating age-related hearing loss should be developed. ARHL accounts for the main hearing impairment with features of pathological variations of central and peripheral auditory systems. Animal models with early-onset ARHL have mild cochlear inflammation, suggesting that inflammation is related to ARHL genesis and progression.<sup>19</sup>

Meanwhile, Seicol et al found that the central cochlear nucleus is activated during the aging of microglial cells,<sup>20</sup> and the increase of the iconic antibody IBA-1 is significant. Microglial cells proliferated and differentiated, and C1q expression was significantly increased, indicating that ARHL occurrence involved the activation of neuroinflammation and the complement system. Therefore, more treatments targeting the innate immune and complement pathways can offer novel ideas for developing new therapeutic approaches. In addition, the experiment showed that microglial production and increased C1q deposition in middle-aged mice were small,<sup>21</sup> indicating that this time window may be the best period for ARHL treatment. We speculated that administering microglia inhibitors in middle-aged ARHL mouse models may delay or treat ARHL.

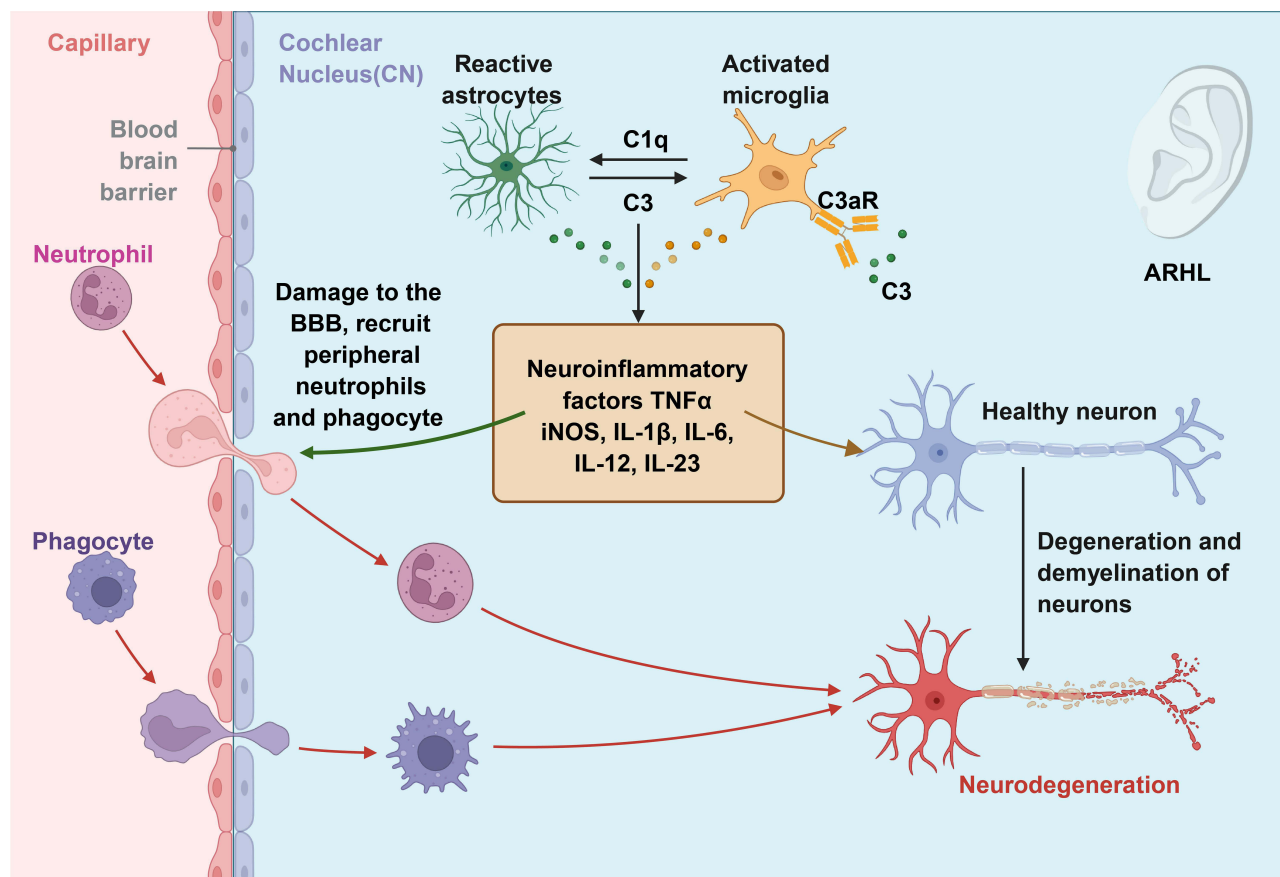
Concurrently, we further studied the pathway mechanism of presbycusis. Current studies showed that microglia activated by injury factors could release complement factor C1q, which critically affects the classical complement system as an initiation factor for the complement pathway.<sup>20</sup> Additionally, C3, located downstream of C1q, also critically affects the complement pathway. Meanwhile, C3 is mainly produced via activated astrocytes,<sup>22</sup> which also target C3aR on the microglial cell surface. In addition, studies on microglia suggested that the complement pathway can be used as a novel therapeutic target. This complement system activation increases the risk of further activation, causing normal tissue death.<sup>23</sup> These may be impaired in degenerative diseases, providing a mechanism for degeneration. Thus, C1q secreted by microglia and inflammatory factors IL- $\beta$  and TNF- $\alpha$  activates astrocytes and the complement system, which further affects surrounding healthy neurons or tissues, leading to the aggravation of degenerative diseases. Therefore, the complement pathway is considered a new therapeutic direction, with C3 as an important therapeutic target factor (Figure 2).



**Figure 1** By discussing and summarizing the known mechanisms of microglia connections in central and peripheral degenerative diseases, the mechanism of the occurrence and development of degenerative diseases is speculated, which provides new ideas and guidance for exploring other degenerative diseases.

## Microglia and Retinal Degenerative Diseases

Retinal degeneration (RD) is a series of retinal diseases characterized by gradual death and nerve cell loss, such as photoreceptor cells, retinal ganglion cells, or retinal pigment epithelium.<sup>24</sup> Currently, no effective interventions have targeted the apoptotic pathway of degenerative cells in treating RD. Moreover, microglia-mediated inflammatory responses have a critical effect on RD progression. Within the normal retina, microglial cells are usually at rest. As the only innate retinal immune cells, their functions include monitoring and maintaining the retina's microenvironment. However, in the degenerative retina, microglial cells can be activated by injury factors, such as aging, and regulate the homeostasis of the retinal microenvironment through "double action". Additionally, as defense cells, activated microglial cells produce various neuroprotective factors, anti-inflammatory cytokines, phagocytosis, etc., to improve and maintain



**Figure 2** During age-related hearing loss progression, activated microglia can release inflammatory factors that destroy the blood–brain barrier and recruit peripheral macrophages into the center. Meanwhile, the released inflammatory factors can also directly act on neurons and cause neuronal degeneration. Concurrently, complement pathway activation may be another key factor in enhancing neuroinflammation. The flowchart was created using Biorender.com.

the retinal microenvironment. By contrast, microglial over-activation can produce various pro-inflammatory cytokines, worsen the retinal microenvironment, and aggravate the apoptosis of nerve cells.<sup>25</sup> Therefore, regulating the activation of degenerative retinal microglial cells is an important strategy to protect nerve cells and delay RD progression. Moreover, microglial cells can clear synapses and other neural elements through complement regulation and delay abnormal neurogenesis and visual function degeneration during retinal senescence and degeneration.<sup>26</sup> CX3CR1 and its ligand CX3CL1 regulate microglia through RAS-guided signal transduction pathways to exert their effects on neurons and retinal cell tissues.<sup>27</sup> Continuous exploration and research on CX3CR1 and its ligand CX3CL1 from multiple perspectives will provide important research directions and ideas for retinal degenerative diseases and provide a novel research target to prevent and treat retinal degenerative diseases.<sup>28</sup> This suggests that microglia can impact the occurrence and progression of RD through the Ras pathway, and inhibiting excessive microglia activation may be an effective strategy to delay RD development.

## Microglia and Alzheimer's Disease

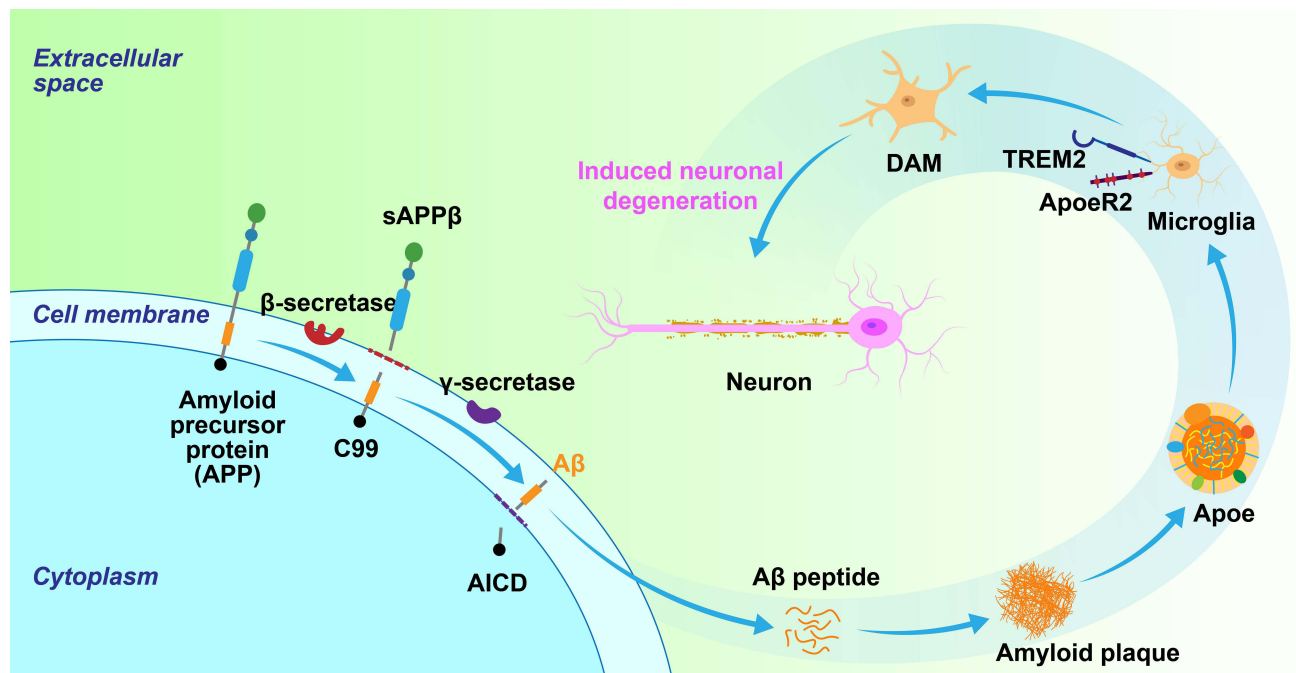
Alzheimer's Disease (AD) accounts for major disease-causing dementia in the world.<sup>29</sup> Many studies showed that aging is the most important factor related to the pathology of neurodegenerative disorders, such as AD.<sup>30</sup> Consequently, understanding microglial alterations during aging stimulation is necessary to prevent and treat these diseases. Microglia also have a dual role within AD. Generally, microglia can protect the brain because they are defense cells maintaining tissue homeostasis through phagocytosis and clearing amyloid-beta peptide (A $\beta$ ) extracellular space, thereby preventing AD.<sup>31</sup> With A $\beta$  accumulation, microglial cells continuously exert A $\beta$  aggregate phagocytosis and removal functions. Still, A $\beta$  aggregates are compacted into dense core plaques before isolation from the neurons when microglia

functions exceed their ability to remove them.<sup>32</sup> This protection involves microglial activation into the disease-associated microglia (DAM) state, determined by apoE and acting in triggering receptor expressed on myeloid cells 2 (TREM2).<sup>33</sup> Moreover, genetic factors and aging may lead to abnormal microglial cell function and may not prevent AD genesis and progression. Toxic amyloid protein (tau) pathological accumulation, especially within injured or stressed neurons, induces the overactivation and inflammation of microglial cells, where phagocytic synapses are released, neuron-damaging neurotoxic factors are secreted, and tau pathological transmission is transmitted.<sup>34</sup> The vast majority of cells in the human body can secrete exosomes. Exosomes have become an important vehicle for signaling between cells. Hirohide Asai et al used a model of adenovirus showed microglia spread tau via exosome secretion, and inhibiting exosome synthesis significantly reduced tau propagation in vitro and in vivo.<sup>35</sup> Clarifying the relationship between harmful proteins such as tau and microglia metabolism will help people better understand the crosstalk mechanism between neurons and microglia. Microglia have a dual role in the AD pathogenic model. Harmful microglia populations appear in the disease's later stages, consistent with synaptic elimination and neuronal degeneration.<sup>36</sup>

Moreover, microglia may represent a new target to delay or halt AD evolution due to recent progress in exploring underlying major mechanisms, exosome, neurodegeneration, plasticity regulation, and synaptic pruning microglia depletion (Figure 3).

## Microglia and Parkinson's Disease

Parkinson's disease (PD) can be caused by abnormal accumulation of alpha-synaptic nucleoproteins, or alpha-syn aggregates, within dopaminergic neurons of the substantia nigra.<sup>37</sup> Many hypotheses exist on PD genesis and progression, and neuroinflammation has an important effect on the neurodegenerative pathogenic mechanism of PD. Microglial cell-induced neuroinflammation is particularly associated with PD pathogenic mechanism.<sup>38</sup> Such neuroinflammatory neurodegeneration is related to microglial activation and up-regulated pro-inflammatory factors.<sup>39</sup> Chronic microglia activation in patients with PD may produce increased pro-inflammatory and cytotoxic cytokine levels, such as IL-6, TNF- $\alpha$ , ROS, etc., resulting in disease exacerbation. These molecules can mediate effective antigen presentation by CD4 +T cells through the major histocompatibility complex(MHC) class II pathway, causing cell differentiation and growth, followed by slow degeneration and, eventually, neuron death.<sup>40,41</sup>



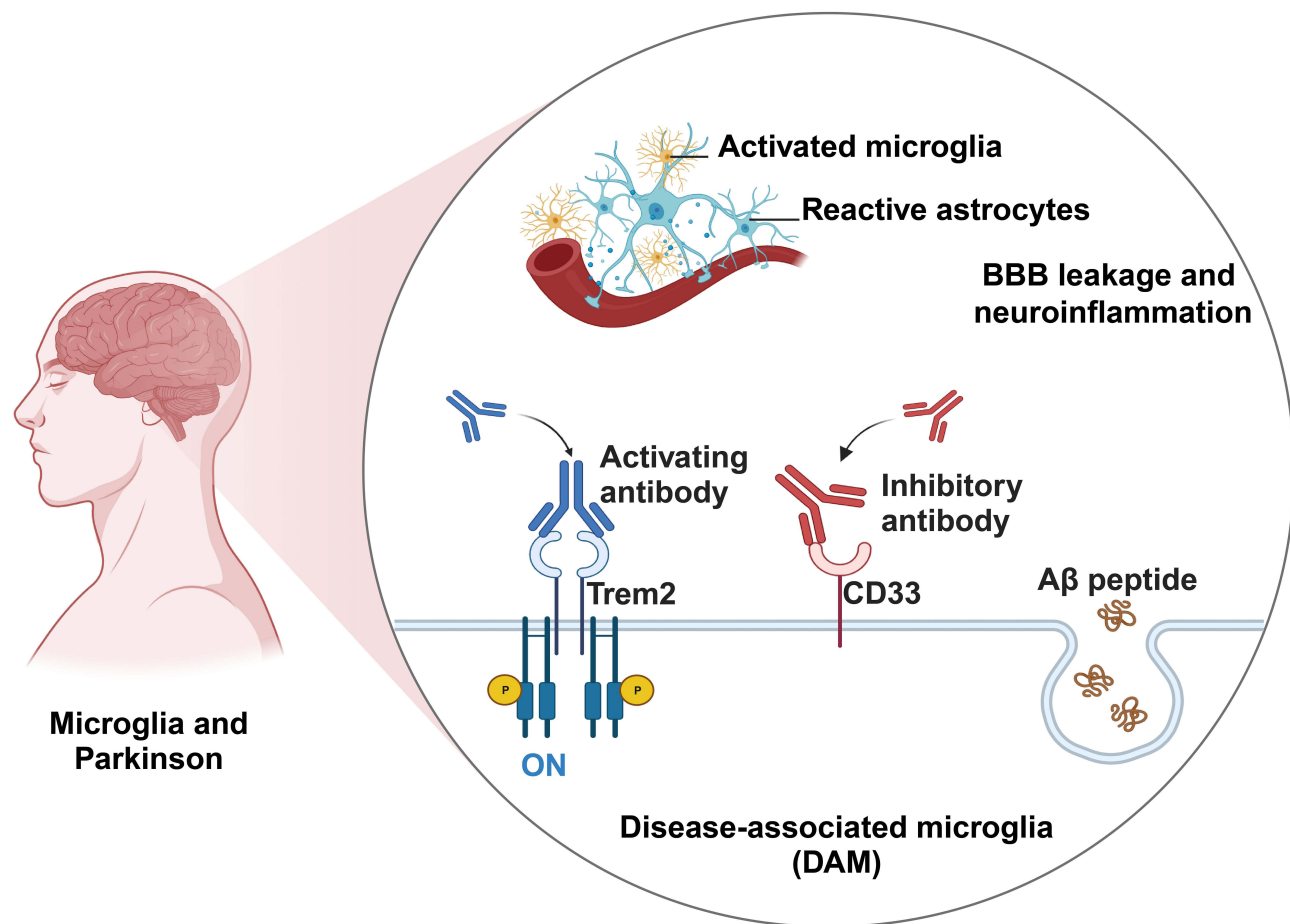
**Figure 3** In Alzheimer's disease, microglia phagocytosis clears A $\beta$  aggregates. This protective mechanism involves microglial activation in the DAM state, determined by TREM2, assisted by apoE. Eventually, it acts on neurons and causes neuronal degeneration.

Moreover, microglia are major intracerebral resident immune cells that normally phagocytose dead cells while clearing misfolded alpha-syn aggregates during PD.<sup>42</sup> However, alpha-syn activates microglia, leading to pro-inflammatory factor release. Recently, microglia can effectively generate exosomes, part of antigen presentation and production mechanism.<sup>43</sup> These microglial cell-derived exosomes can critically affect alpha-syn transmission, inducing alpha-synaptic nucleoprotein aggregation within neurons,<sup>44</sup> thereby inducing degeneration of the substantia striatum, indicating such exosomes play an important role in PD pathology. Similar to the TREM2 mechanism within AD, TREM2 significantly affects the transformation of M1 microglial cells with pro-inflammatory phenotypes into M2 phenotypes, which benefits PD immunopathogenesis.<sup>45,46</sup> Therefore, chronic microglial activation in patients with PD may produce excessive pro-inflammatory and cytotoxic factors, thereby exacerbating the disease. By contrast, we identified the neuroprotective effect of microglial cells, which plays a major role in clearing alpha-syn nucleoproteins released by neurons.

In conclusion, PD is closely associated with microglia, and the chronic activation of microglia is also responsible for the development of chronic neuroinflammation in PD. Simultaneously, injury-induced microglia can impact the progression of PD through its polarization (M1/M2). Furthermore, the secretion of microglial exosomes also presents novel prospects for diagnosing and treating PD. (Figure 4).

## Microglia and Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) accounts for an adult-onset neurodegenerative disorder characterized by rapid progression showing selective destruction of upper/lower motor neurons, leading to limb muscle tissue atrophy and weakness in varying levels, spasm, conformation disorders, and dysphagia.<sup>47</sup> Neuroinflammation, such as T-cell infiltration



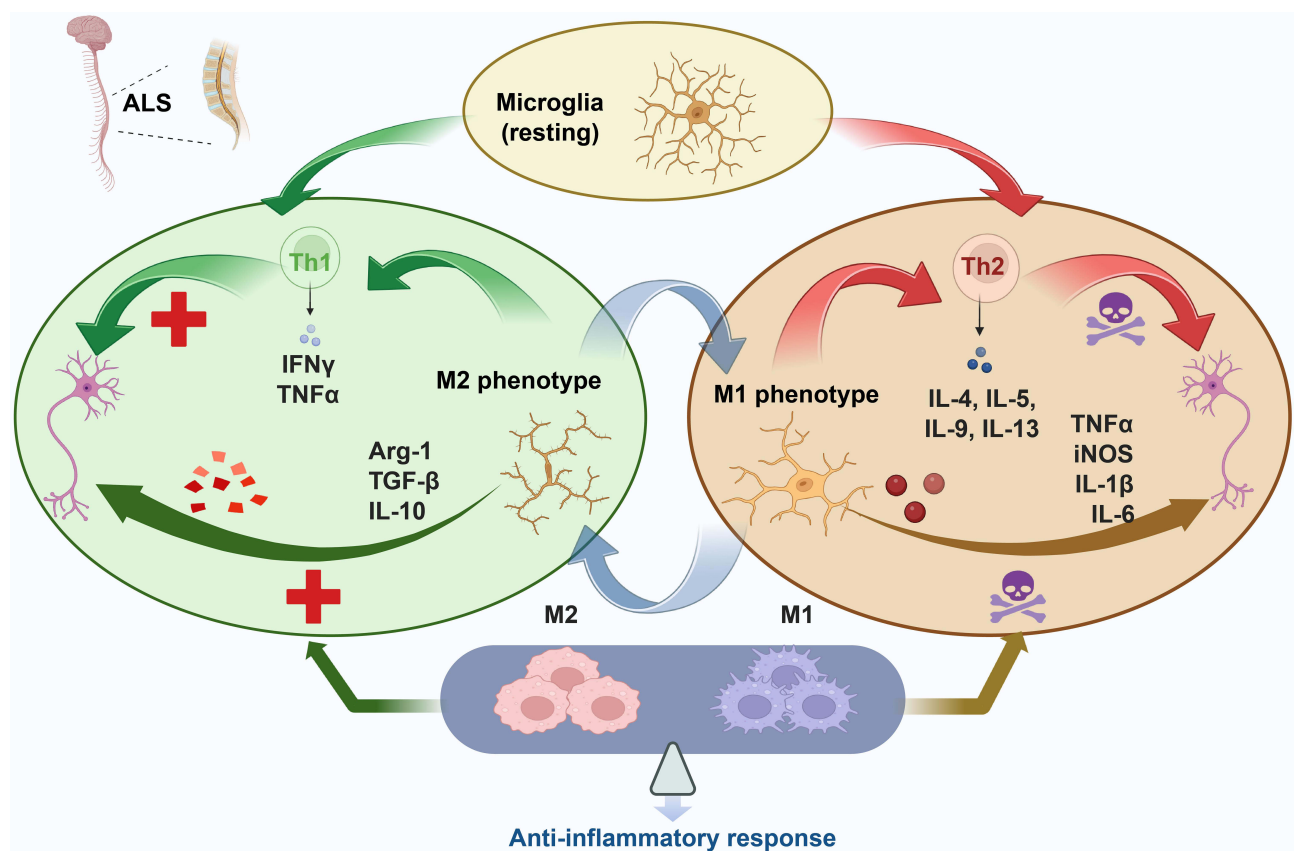
**Figure 4** Microglia will engulf abnormal neurons and alpha-syn aggregates, whereas over-activation will become a DAM state, causing neuroinflammation and eventually leading to PD. This also reflects the dual role of microglia. The flowchart was created using Biorender.com.

or microglial activation, represents a neuropathological marker for ALS. Traditionally, immune function in patients with ALS was considered dominant in CNS inflammation, but neuroinflammation has been currently considered as the major characteristic shared by different classical neurodegenerative diseases.<sup>48</sup> Neurochemical or morphological studies showed that ALS microglial cells are activated and proliferated.<sup>49</sup> Microglial activation was observed in relevant brain domains in patients with ALS, and microglia proliferated with increasing disease severity. Neuronal damage models showed that microglial cell activation also plays a dual role in ALS, promoting neuronal protection and damage. Moreover, microglial cells exhibit functional changes during activation, including cell count, morphology, cytokine and growth factor generation, and surface receptor levels. This indicates that microglial cell activation status changes due to signals in damaged neurons and adjacent glial cells. Like macrophages, microglial cells may display alternative activation or inactivation of the M2 phenotype or classical activation of the M1 phenotype in ALS.<sup>50,51</sup> M2 microglial cells may suppress pro-inflammatory cytokine production, contribute to inflammation regression using endocytic clearance, produce increased IGF-1, IL-4, and IL-10, accelerate tissue repair, and promote Th2 function, enhancing neuron survival. Exosomes derived from microglia have the potential to disseminate pathogenic factors. For instance, the secretion of SOD1 by NSC-34 Motor Neuron-Like Cells in hSOD34G1A overexpressing mice can promote inflammation and impact neuronal survival (Figure 5).<sup>52</sup>

Therefore, the dual role of microglial and T cells may protect neurons by regulating beneficial M2 microglial inflammatory responses in chronic neurodegenerative models of ALS, leading to slower disease progression. Similarly, microglial exosomes also evidence a well-coordinated and complicated dialog between ALS neurons, microglial cells, and T cells.

## Microglia and Multiple Sclerosis

Multiple sclerosis (MS) is a chronic inflammatory CNS disorder, and its pathological and clinical manifestations were initially identified by Jean-Martin Charcot in 1961.<sup>53</sup> Unlike other degenerative diseases, the cause of neuron mortality

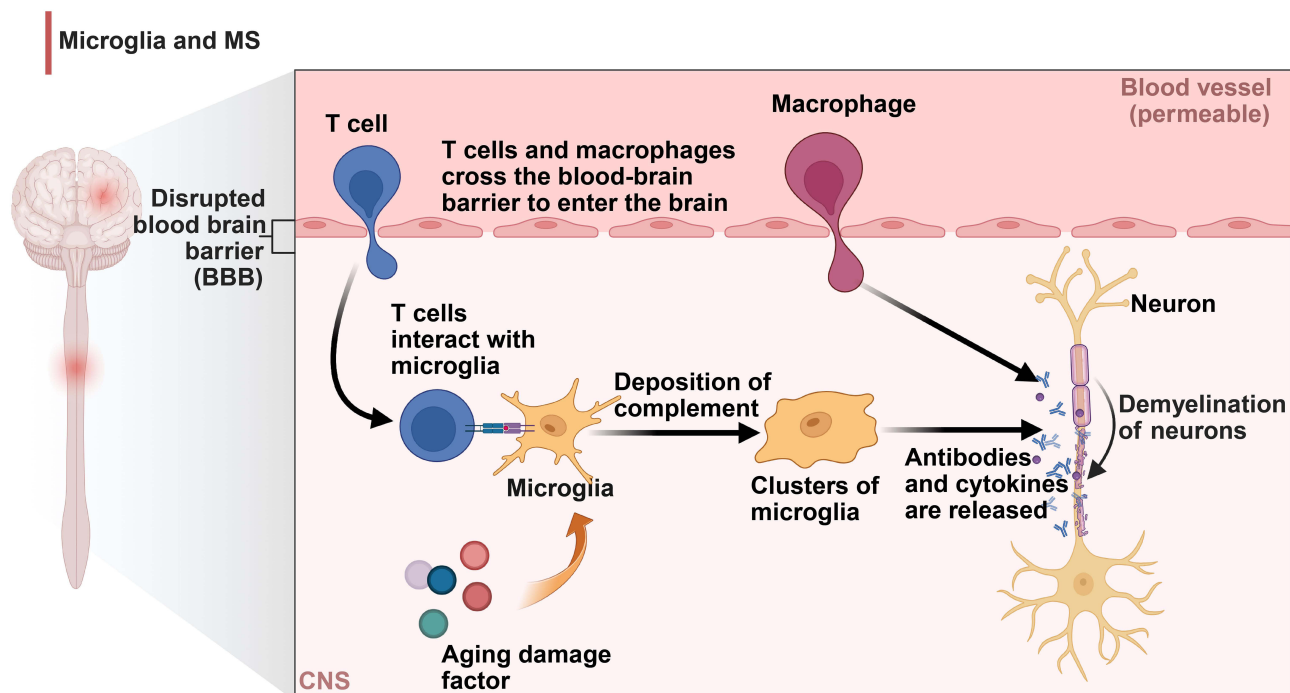


**Figure 5** In ALS, microglial cells not only play a role through different polarization states but also present antigens to different T cells to affect neurons. The flowchart was created using Biorender.com.

during MS was secondary to decreased reactive T-cell activation due to decreased function of targeted myelin.<sup>54</sup> Nonetheless, such neurodegenerative diseases exhibit the characteristics of gradual neuron loss associated with cognitive impairment and motor dysfunction, which are related to inflammatory and immune responses. The neuroinflammatory process in MS is similar to other neurodegenerative diseases. The pathology of MS is better understood in studies of other neurodegenerative disorders.

Microglia plays a vital role in molecular recognition during MS. In cases of aging, irritation, bacteria, or injury sign, microglial cells are rapidly activated and migrate toward the injury site. However, activated microglial cells also exhibit neurotoxic effects in MS, despite their altered state and function to protect the CNS.<sup>55,56</sup> Microglial activation is not limited to the lesion area, and patients with MS have more pronounced microglial activation in normal white matter compared with healthy controls.<sup>57</sup> In addition, clusters of activated microglia, known as microglia nodules, are gradually deposited during axon degeneration, oligodendrocyte activation, or complement pathway product activation.<sup>58,59</sup> In MS, activated C3 and C1q levels are up-regulated within the hippocampi, which are localized in synapses in lysosomes and microglia, indicating microglial cell-induced synaptic phagocytosis and removal.<sup>60</sup> These microglia nodules exhibit characteristics of insufficient demyelination and leukocyte infiltration, finally developing into active demyelinating MS lesions. Furthermore, microglial cells mainly exhibit pro-inflammatory phenotypes within early active lesions, which begin to be expressed and are related to inflammatory factor secretion, oxidative damage, phagocytosis, T-cell stimulation, and antigen presentation. Apart from acute lesions, activated microglia are observed in the lesion extension of chronic and slow-progressing MS lesions, which continuously produce inflammatory factors causing chronic damage. Thus, these results render microglial cells in the core of MS pathology, and microglia are stimulated by damage factors and regulated by the immune system to produce pro-inflammatory behavior, which is critical in MS pathogenesis.

Therefore, effective utilization of the dual role of microglia to regulate their polarization characteristics and fully use their regulatory effect of the complement pathway to limit and reduce potential reactions promoting that promote degeneration, protect the CNS from damage, and promote local recovery (Figure 6).



**Figure 6** In MS, microglia can affect neurons through phagocytosis through microglial cluster formation that destroys myelin sheaths. The flowchart was created using Biorender.com.



Therefore, from the above examples of microglia, it is not difficult to find that although the function of microglia in each disease state is complex, but the dual role of microglial cells under different activation states plays an important role in central nervous system degenerative diseases.

## Microglia and Peripheral Nervous System (PNS) Degenerative Diseases

Aging is an inevitable biological process characterized by neurological dysfunction, such as emotional and cognitive decline. Aging is associated with neuroinflammation, neurodegeneration, amyloid plaque deposition, dementia, and neuropsychiatric diseases in CNS.<sup>61</sup> In addition, aging affects the PNS to varying degrees. For example, pain neuron excitability in the lumbar dorsal horn was significantly enhanced in older rats than younger ones.<sup>62</sup> Therefore, aging may also be a key factor leading to degenerative abnormalities in signal transduction between pain-sensing neurons. Microglial cell activation can effectively regulate the excitability of pain-sensing neurons within the spinal dorsal horn to cope with the occurrence of PNS diseases, such as sciatic nerve injury.<sup>63,64</sup> Our understanding of the effect of microglial cells on CNS degenerative disorders, particularly their dual role, further explores the important function of microglial cells on PNS degenerative diseases.

Chronic pain in osteoarthritis (OA), characterized by pain sensitization, is a common pain and disabling disorder worldwide. Additionally, it represents PNS degenerative disease with a high incidence. OA involves peripheral and central mechanisms, and spinal microglial cell and synovial macrophage hyperactivity are the basis for the pain sensitization mechanism of OA in CNS and PNS.<sup>65</sup> Hahm et al concluded that analgesic tolerance of OA pain control induced by repeated electrical stimulation and changes in microglial cell activation are related.<sup>66</sup> Microglial cells are also present in the caudate subnucleus of the spinal cord of the trigeminal nerve (Vc) and the upper part of the cervical spinal cord (C1/C2). Thus, microglial cell activation within Vc and C1/C2 can be related to the pathology of oral and facial pain hypersensitivity.<sup>67,68</sup> Studies on accelerated susceptibility to aging (SAMP8) mice and anti-aging control (SAMR1) mice showed that microglial cells play an important role in the periphery through the mutual transformation of M1 and M2,<sup>69</sup> thereby causing the development of degenerative diseases. IL-10 and TNF- $\alpha$  modulate pro-inflammatory circulation and polarity change in activated microglial cells into M1/M2 macrophages.<sup>70</sup> In addition, reduced IL-10 levels similarly promote microglial polarization into M1 in the pro-inflammatory environment.<sup>71</sup> Consequently, the mechanism of microglia phenotype change may not be independent but interrelated, and it is a key factor in maintaining M1/M2 polarized balance to promote aberrant oral and facial pain while delaying OA pain. In summary, aging injury-induced age-related neuroinflammation affects activated microglial cell polarity variation and enhances neuronal excitability at microglial aggregation sites, such as Vc and C1/C2. These findings may provide useful information in exploring the influence of aging damaging factors on the development of PNS neurodegenerative disorders.

In summary, the microglial cell polarization state has a critical effect on PNS degenerative diseases. How to effectively control microglial activation may be the key to treating degenerative diseases in the future.

## Relationship Between Microglial Inhibition and Activation and Degenerative Diseases

### Microglia and CSF1R Inhibitors

Microglia modulate the architecture of adult neurons, and signals from colony-stimulating factor 1 receptor (CSF1R) determine adult microglia regulation.<sup>72</sup> CSF1 is important in modulating macrophage growth and differentiation.<sup>73</sup> Moreover, mice lacking CSF1 or CSF1R showed decreased density of macrophages in several tissues, and neurons showed demyelination and other neuronal degeneration symptoms.<sup>74</sup> Excessive pruning and even eliminating synapses are common essential characteristics of numerous disorders with excessive microglial proliferation and differentiation, such as AD, ARHL, etc.<sup>75,76</sup> CSF1R inhibitors, which can cross the blood-brain barrier, rapidly remove microglial cells in the CNS while inhibiting microglia continuously. In addition, studies showed that CSF1R inhibitor treatment significantly increased the density of dendritic spines and synaptic points in all brain regions tested in microglia-lacking adult mice.<sup>77</sup> Concurrently, chronic microglial cell depletion can increase the stability of perineuronal networks

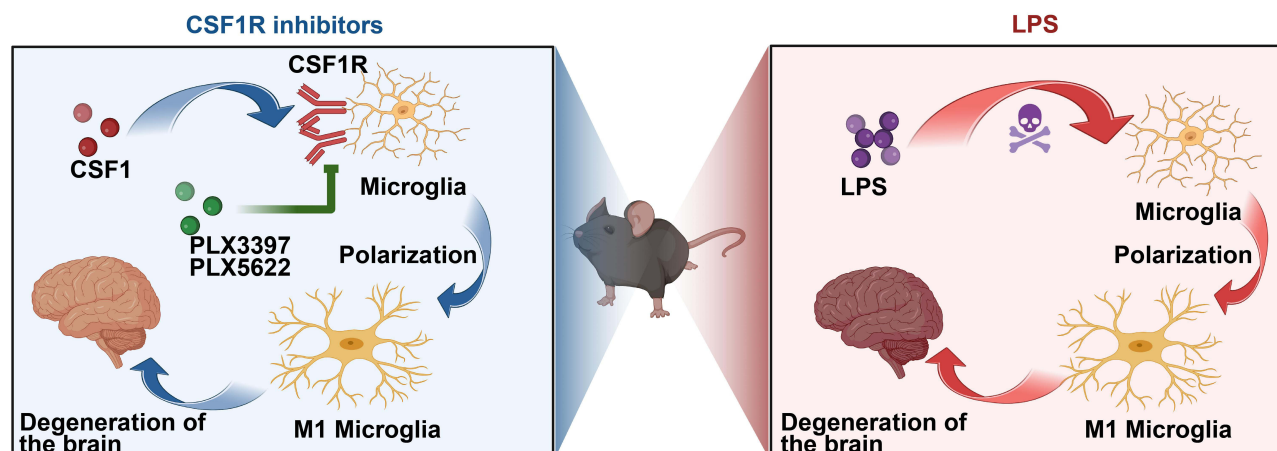
and enhance local inhibitory/excitatory circuit connections with excitatory neurons.<sup>78</sup> Therefore, neurons can better play the signaling function by inhibiting microglia, reducing the occurrence and development of degenerative diseases.

PLX3397<sup>79</sup> and PLX5622<sup>80</sup> are the most well-known CSF1R inhibitors. Mice fed with both showed whole-body microglia inhibition,<sup>81,82</sup> and their incidence of degenerative diseases greatly reduced, such as AD,<sup>75,83</sup> further confirming the critical effect of microglia on degenerative diseases. Meanwhile, Elmore et al measured measuring PLX3397 levels within the brain tissue and showed continued microglia cell elimination during a medication withdrawal. However, trace amounts of microglia were detected 1 day after drug withdrawal and recovered to normal levels on the 7th day of recovery,<sup>84</sup> indicating that CSF1R inhibitors continuously act on microglia, leading to its clearance in the brain and effectively alleviate degenerative diseases without causing permanent damage. By contrast, several studies suggested that activating microglia to produce neuroinflammation can promote the development of degenerative disorders, such as PD.

## Microglia and Activators

Neuroinflammatory response is related to neurodegenerative diseases, and microglial cells are resident immune cells within the CNS, whose activation promotes neuroinflammation in neurodegenerative diseases. Lipopolysaccharide (LPS), as an excellent pro-inflammatory agent, provides a good basis for studying neurodegenerative diseases.<sup>85,86</sup> LPS is closely related to microglial activation. Microglial cells are key nervous system-specific immune cells with various phenotypes, which can metastasize to maintain tissue homeostasis. Additionally, microglial cells exhibit common and specific characteristics in phenotypic polarization relative to peripheral macrophages. LPS is a typical bacterial-derived endotoxin that directly activates microglia through toll-like receptor 4,<sup>87</sup> which may cause and amplify neuroinflammation and influence various neurodegenerative diseases. Microglial activation can sustain the increase in immunoreactivity with the microglia-specific antibody iba-1.<sup>88</sup> Kondo et al evaluated glial activation after LPS administration and observed morphologic changes in microglia 2 days after LPS administration, with partial recovery within 1 week but long-lasting.<sup>89</sup> Thus, the role of LPS in microglial activation is long-lasting. LPS stimulates the polarization of microglial cells for producing various inflammatory factors, including TNF- $\alpha$  and IL- $\beta$ , while activating neuronal degeneration and loss of neuronal function due to persistent neuroinflammation, eventually leading to degenerative diseases.

Coincidentally, the CSF1R antagonist impaired the potential coupling between microglia and astrocytes in mice subjected to microglial pharmacological ablation using PLX5622. In contrast, priming microglial cells with LPS increased synaptic transmission after induction, further enhancing communication with astroglia.<sup>90</sup> Signaling between glial cells to promote neuroinflammation is the key to developing affective disorders in many neurodegenerative diseases, suggesting that microglia are crucial for developing degenerative diseases (Figure 7).



**Figure 7** Microglia treated with CSF1R inhibitor and LPS mouse models showed different changes. Microglia in mice treated with the inhibitor significantly decreased, and the onset of degenerative disease was delayed, whereas microglia in mice treated with LPS showed proliferation and differentiation, accelerating the onset of degenerative disease. The flowchart was created using Biorender.com.

Neurodegenerative diseases are effectively controlled after using inhibitors. By contrast, activators may aggravate neurodegenerative diseases, indicating that microglial cells are closely related to degenerative diseases. They can be used as a target for the treatment of degenerative diseases.

## Discussion

The function of microglia is complex, and the states of microglia are different under various conditions, which is difficult to discuss uniformly. This review focuses on the disease state and explores the commonality of one aspect of its complex manifestations so as to provide constructive guidance for the pathogenesis and treatment strategies of other types of degenerative diseases in the future. Microglial cells critically affect CNS degenerative diseases, such as AHRL, retinal degenerative diseases, AD, and PNS degenerative diseases, such as decreased sensitivity to pain caused by aging. Microglial cells affect disease genesis and progression because of its dual role and other complex mechanisms. Additionally, microglial cells can also activate astrocytes through cascaded amplification, further stimulating neuronal degeneration and leading to the generation of degenerative diseases. For example, in AD and PD brains, microglial cells and astrocytes can acquire active inflammatory phenotypes, efficiently phagocytize accumulated cell debris and proteins, and produce different inflammatory factors and cytokines. The astrocyte–microglial cell interaction triggers reactive astrocytes. Astrocytes may have a common molecular language with microglia within diverse disorders, such as neuroinflammatory mechanisms and complement pathway mechanisms. As technology advances, astrocyte–microglial cell interaction may become a precise and efficient target for disease treatment. In most instances, microglia and astrocytes operate harmoniously and complementary across a broad spectrum of pathophysiological processes. These processes encompass synaptic phagocytosis and remodeling, the regulation of the blood-brain barrier, maintenance of homeostasis, and involvement in immune responses. Disturbance in astrocytoma–microglia interaction leads to the development of degenerative diseases.

In summary, the commonality of microglia as the target of degenerative diseases has not been thoroughly discussed. In this review of CNS and PNS degenerative diseases, we found that these diseases activate microglial cells through aging and other damage factors and regulate their polarized phenotypes (M1/M2) that play dual roles in regulating the genesis and progression of degenerative disorders. Moreover, microglial cells can also impact the occurrence of degenerative disorders, such as AD, PD, through complement pathway activation and exosome secretion.<sup>91</sup> There is a close link between exosomes and the polarization of microglia, and exosomes such as microRNA play a regulatory role in the M1/M2 polarization of microglia.<sup>92</sup> Microglial exosomes can be transported to and taken up by neurons, which may be beneficial or harmful in central nervous system diseases. Microglial cells have an important effect on phagocytic synapses, particularly in MS and AD. Moreover, they exert a dual effect on PNS neurodegenerative disorders, such as the decline of pain-sensing neurons and OA. Similarly, the crosstalk between microglia and astrocytes should be considered. Damage factors from aging and other factors activate microglia to produce inflammatory factors, such as TNF- $\alpha$  and complement factors, including C1q, to activate astrocytes further, and this pro-inflammatory circulation between glial cells also promotes the development of degenerative diseases.

## Further Directions and Limitation

Another innovation of this paper is the incorporation of microglia agonists and inhibitors in the discussion to explore potential treatments for neurodegenerative diseases. The management of neurodegenerative diseases has always posed a challenging problem within the medical community, and our fundamental research aims to provide effective treatment options for the numerous patients worldwide suffering from these conditions. The establishment and application of animal models have significantly advanced the medical field for most researchers. Model tests have led to the development of numerous targeted drugs and treatments. Among neurodegenerative diseases, Parkinson's disease animal model is the most well-known and mature.<sup>93–95</sup> The use of this model has yielded unexpected progress in exploring treatment options for Parkinson's disease, providing valuable reference experience.<sup>96–98</sup> This prompts us to consider whether microglia inhibitors could effectively delay PD progression when applied on a mature PD model, which may also extend to other degenerative diseases.

Microglia activators like lipopolysaccharide can directly activate microglia into an M1 pro-inflammatory form while also enhancing interaction between microglia and astrocytes, thereby inducing neuroinflammation that leads to neurodegenerative diseases. Conversely, microglia inhibitors specifically counteract chronic activation of systemic microglia without causing organic lesions. Therefore, continuous administration of microglial inhibitors may also exert a positive inhibitory effect on degenerative diseases in elderly individuals. However, exploring how we can ensure that both inhibitors and activators maintain their normal physiological effects after acting upon microglia itself remains crucial. This suggests that further study should focus on refining pathways or surface receptors associated with microglia; for instance, investigating the use of C3aR inhibitors to inhibit the C3a receptor on the surface of microglia selectively could not only block chronic activation but also preserve most functions of these cells—an avenue worth exploring. Future studies should continue broadening the horizon and explore the relationship between glial cells and degenerative diseases to find new opportunities for treating degenerative diseases.

This review also has limitations; the state of microglia in different states can not be generalized. This article mainly discusses microglia in disease states, and the crosstalk between glial cells cannot be ignored. When we explore the connectivity and relationship between microglial cells and degenerative diseases, their interaction with other glial cells should be considered. This study focused on only a small portion.

## Conclusion

Therefore, we clarified that the dual role of microglia is the key point of communication in CNS and PNS degenerative diseases, and exosome and complement pathways provide us with ideas, especially in ARHL. Current data show the importance of the complement pathway, particularly C3 and C3aR. In conclusion, it is hoped that this review of microglia in disease state can provide good ideas and suggestions for exploring unknown degenerative diseases. In the future, When studying neurodegenerative diseases with unknown mechanisms, focusing on the dual role of central microglia may receive unexpected gains, and we may be able to control the activation states of the microglial cell, exosome, and complement pathways, thereby reducing the occurrence of degenerative diseases and achieving therapeutic effects.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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