Microglial response to aging and neuroinflammation in the development of neurodegenerative diseases

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Abstract

Cellular senescence and chronic inflammation in response to aging are considered to be indicators of brain aging; they have a great impact on the aging process and are the main risk factors for neurodegeneration. Reviewing the microglial response to aging and neuroinflammation in neurodegenerative diseases will help understand the importance of microglia in neurodegenerative diseases. This review describes the origin and function of microglia and focuses on the role of different states of the microglial response to aging and chronic inflammation on the occurrence and development of neurodegenerative diseases, including Alzheimer's disease, Huntington's chorea, and Parkinson's disease. This review also describes the potential benefits of treating neurodegenerative diseases by modulating changes in microglial states. Therefore, inducing a shift from the neurotoxic to neuroprotective microglial state in neurodegenerative diseases induced by aging and chronic inflammation holds promise for the treatment of neurodegenerative diseases in the future.

Key Words: aging; Alzheimer's disease; cytokines; Huntington's disease; microglia; neurodegenerative diseases; neuroinflammation; neuroprotection; neurotoxicity; Parkinson's disease

From the Contents

Introduction

Neurodegeneration is caused by various factors such as aging, oxidative stress, inflammation, abnormal protein accumulation, excitotoxicity, and metal overexposure followed by neuronal degeneration and death in specific regions of the central nervous system (CNS) (Dugger and Dickson, 2017; Chib and Singh, 2022). Among these, cellular senescence and chronic inflammation in response to aging are considered to be indicators of brain aging, have a significant impact on the aging process, and are the main risk factors for inducing neurodegeneration (Franceschi and Campisi, 2014; Lasry and Ben-Neriah, 2015). The primary neurodegenerative diseases commonly seen in the older adults are Alzheimer's disease (AD), Huntington's disease (HD), and Parkinson's disease (PD) (Hou et al., 2019). These diseases cause cognitive decline in patients, significantly affecting their daily lives, and burdening their families and society. This burden continues to increase due to the rapid aging of the population and limited treatment strategies. Despite the ongoing exploration of neurodegenerative diseases, cures for these diseases have yet to be found. With advances in the field of genome editing, clustered regularly-interspaced short palindromic repeat (CRISPR) technology is being considered for the treatment of neurodegenerative diseases (Raikwar et al., 2019); this plays an essential role in slowing the progression of neurodegenerative diseases, such as AD, HD, and PD, by halting or delaying the progression of neuroinflammation as well as neurodegeneration (Chitnis and Weiner, 2017; Qin et al., 2021). However, as this technique is still under development, its clinical effectiveness and safety have not yet been proven. Therefore, the development of effective treatments and interventions to slow the progression of the disease is urgent. However, it is essential to consider the role of senescence and inflammatory mechanisms in the pathogenesis and progression of neurodegenerative diseases to prescribe the correct remedy.

The aging of an organism drives impaired biological function, reduced synaptic plasticity, abnormal neuronal activity, dysregulation of neuronal Ca^{2+} homeostasis, and inflammation in brain cells. These changes further impair the memory, learning, cognitive exploration, coordination, and motor abilities of the organism (Mattson and Arumugam, 2018; Levite, 2023), and contribute to neurodegenerative diseases in the aging brain.

Inflammation is a protective mechanism in the body that maintains homeostasis in the brain's internal environment by repairing, regenerating, and removing damaged tissues/cells or infection factors, parasites, and toxins from the body (Kulkarni et al., 2016; Shi et al., 2023). However, inflammation, as a concomitant response to cellular senescence and organismal aging, also plays a vital role in promoting organismal aging. During aging, damage to the innate and acquired immune systems of the organism occurs, resulting in a functional imbalance of the immune system. The engagement of these immune systems leads to the clearance of pathogens, damaged tissues, and senescent cells, and causing an increase in the expression of pro-inflammatory cytokines (e.g., tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, IL-6, IL-8, reactive oxygen species (ROS), C-C motif chemokine ligand (CCL)-2, and CCL-5), which promote an inflammatory response (Teissier et al., 2022). Chronic stimulation of these factors not only leads to a chronic, low-grade, micro-inflammatory senescence state in the organism, but also induces neuroinflammation and causes neuronal damage, leading to age-related neurodegeneration (Kempuraj et al., 2016; Shabab et al., 2017).

Microglia are resident immune cells in the brain. In normal physiological states, they can promote brain development, repair cellular damages, protect against inflammation, and promote neuronal survival, immune surveillance, and neurogenesis, thus maintaining the homeostasis of the brain's internal environment (Sierra et al., 2010; Tremblay et al., 2010; Eyo and Dailey, 2013; Pierre et al., 2017; Qiu et al., 2023). However, in pathological states, microglia are over-activated in response to disease factors, resulting in an excessive inflammatory response within the brain (Azam et al., 2021). A sustained inflammatory response limits the beneficial functions of microglia and exerts neurotoxic effects by increasing the release of inflammatory cytokines and inhibiting neural regeneration (Russo and McGavern, 2016). More importantly, with the aging process, misfolded proteins, cellular debris, and other inflammatory stimuli accumulate in the brain, inducing continuous stimulation of the microglia and accelerating the aging process.

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The increased level of aging in the organism further leads to a decrease in the phagocytic potential and surveillance capacity of microglia, triggering a vicious cycle that increases the production of inflammatory substances harmful to neuronal health (Villa et al., 2016) and promotes the development of neurodegenerative diseases (Kim et al., 2022). Therefore, reversing neurodegeneration caused by neuroinflammation can effectively mitigate the progression of neurodegenerative diseases.

Microglia-mediated neuroinflammation is currently considered a hallmark of several CNS diseases. Influencing the functional microglial states is a promising method to treat neurodegenerative diseases; however, the mechanisms by which microglia influence the developmental progression of neurodegenerative diseases caused by senescence and neuroinflammation need to be further explored. In this review, we will elucidate the role of microglia in aging and inflammation, focusing on the role of microglia in the development of neurodegenerative diseases and providing new ideas for the treatment of neurodegenerative diseases.

Search Strategy

References for this narrative review were searched from the PubMed database. The time frame for the search was 1999–2023 and the retrieval strategies are shown below: (neuroinflammation[Title/Abstract]) AND (drug[Title/Abstract]) AND (microglia[Title/Abstract]) AND ("Neurodegeneration"[Title/Abstract]) OR (Parkinson disease[Title/Abstract]) OR (Parkinsons[Title/Abstract]) OR (PD[Title/Abstract]) OR (Parkinson's disease[Title/Abstract]) OR (Alzheimer's disease[Title/Abstract]) OR ("Alzheimers disease"[Title/Abstract]) OR (AD[Title/Abstract]) OR (Huntington's disease[Title/Abstract]) OR (Huntingtons disease[Title/Abstract]) OR (HD[Title/Abstract]).

Aging and Inflammation

Cells within the brain respond to aging and external stressors with a decline in their normal physiological functions (e.g., substance transport function of cell membranes) and proliferative functions, resulting in a disruption of the usual cognitive abilities of the organism, which may lead to tissue dysfunction and age-related diseases. In the physiological context, senescence plays an essential role in development, tissue regeneration, and tissue repair (Storer et al., 2013; Mosteiro et al., 2016; Davaapil et al., 2017; Walters and Yun, 2020). However, with aging, different cellular stressors (e.g., oxidative stress, DNA damage, and mitochondrial stress) increase, disrupting the homeostatic balance in vivo. Senescent cells exhibit multiple effects and promote tissue aging through intrinsic and extrinsic mechanisms. Intrinsically, if the growth of senescent cells is stalled in the stem cell compartment, it may impair tissue regeneration and promote cellular dysfunction in a non-autonomous manner (Ovadya and Krizhanovsky, 2018; Calcinotto et al., 2019). Externally, senescent cells accelerate tissue aging by secreting IL-1β, IL-1α, IL-8, IL-6, CCL-2, vascular endothelial growth factor (VEGF), transforming growth factor beta (TGF-β), fibrinogen activator (PLAT), as well as matrix metalloproteinase (MMP)-1, -3, and -10, which constitute the senescence-associated secretory phenotype (SASP) (**Figure 1**; Birch and Gil, 2020). SASP is both a consequence of aging and an inducer of aging; senescent cells accelerate their aging process and that of their neighbors by autocrine means, resulting in increased SASP and modulation of immune surveillance of senescent cells, thus altering the local tissue environment and possibly contributing to inflammation (Acosta et al., 2008; Krizhanovsky et al., 2008; Kuilman et al., 2008; Ohtani, 2022). In addition, SASP contributes to tissue repair and the recovery of damaged cells from senescence (Shmulevich and Krizhanovsky, 2021). Since SASP has both beneficial and detrimental consequences, it may serve as an effective double-edged target for pharmacological intervention in human diseases.

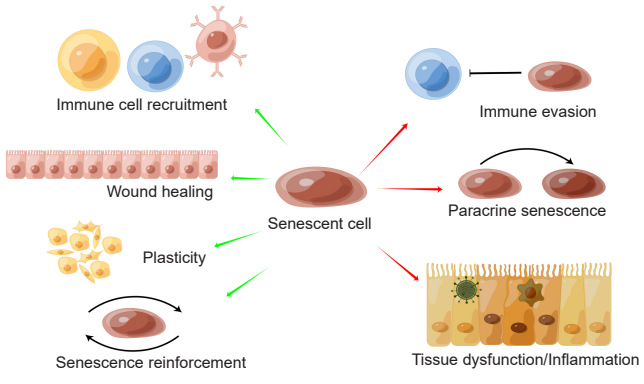

Figure 1 | **Multiple effects of senescent cells.**
Senescent cells can accelerate tissue aging by increasing the production of the SASP, which can also induce further damage senescent cells and promote the senescence of neighboring cells. The left (green) exhibits beneficial effects on the organism, including the recruitment of immune cells and tissue remodeling. The right (red) shows the deleterious effects on the organism, such as immune escape and inflammation. Created with Figdraw. SASP: Senescence-associated secretory phenotype.

The expression of inflammatory mediators is a key feature of aging at the cellular and organismal levels. During aging, uncontrolled age-related immune detection, combined with the immune evasion of senescent cells, leads to a further increase in the number of senescent cells, severely affecting the organism's routine physiological functions (Ovadya et al., 2018; Muñoz et al., 2019). Cellular senescence leads to chronic inflammation in tissues via two main mechanisms: 1) senescent cells amplify SASP through paracrine synergistic effects, thus exacerbating the inflammatory response, or 2) the impaired immune function due to senescence leads to the accumulation of senescent cells, further exacerbating inflammation (Ovadya and Krizhanovsky, 2014; Baker and Petersen, 2018). In addition, chronic inflammation accelerates organismal aging through oxidative damage, DNA damage, and stem cell senescence (Cavanagh et al., 2012; Colombini et al., 2022; Buzoglu et al., 2023). The adverse effects of senescence on the innate and adaptive immune responses decrease the efficacy of vaccination and increase susceptibility to infectious, chronic, autoimmune, and neurodegenerative diseases (Castelo-Branco and Soveral, 2014). Therefore, improving chronic inflammation caused by aging is beneficial in slowing down the development of neurodegenerative diseases.

A study has shown that microglia protect neurons through immunosurveillance in normal physiological states and have an irreplaceable role in maintaining the homeostasis of the brain's internal environment (Casano and Peri, 2015). However, microglial phagocytosis is impaired in response to chronic inflammation caused by aging; their neuroprotective state is changed to a neurotoxic state via the secretion pro-inflammatory cytokines, leading to neuroinflammation, which further promotes increased accumulation of toxic proteins and accelerates neurodegeneration (Rawji et al., 2016; Sikora et al., 2021). Studies in neuroimmunology have shown that modulating the states and function of microglia during the aging process can improve inflammation (Tang and Le, 2016; Song and Suk, 2017), which is a novel way to slow down the development of neurodegenerative diseases.

Role of Microglia in Neurodegenerative Diseases

Microglia, which are resident macrophages of the CNS, account for 10–15% of neuroglia, and are implicated in the pathogenesis of many neurodegenerative and inflammatory diseases in the brain (Nayak et al., 2014). Pío del Rió Hortega first proposed that mesodermal cells invade the brain to form microglia at the late stage of embryonic development (Hortega, 1918; Del Rio-Hortega and De Estudios, 1920; Kaur et al., 2017). Despite some controversies about whether microglia originate from the mesoderm or the ectoderm (Chan et al., 2007; Ginhoux et al., 2013), some researchers still followed Pío del Rió Hortega's hypothesis and confirmed it by light microscopy analysis and immunohistochemistry (Hortega, 1918; Del Rio-Hortega and De Estudios, 1920; Kaur et al., 2017). In mice, microglia originate from developmentally infiltrated yolk sac red medullary lineage progenitors (Ginhoux et al., 2010), migrate through the blood circulation to the neuroepithelium, and enter the brain parenchyma, forming a blood-brain barrier (BBB) that constitutes a unique microenvironment for microglia.

Microglia are mainly distributed in the spinal cord and brain. As intrinsic immune cells in the brain, their function is regulated by several cells (e.g., neurons, astrocytes, T cells, and the BBB) (González et al., 2014). In addition, microglia constitute the front-line defense of the innate immune system, participating in various immune responses by changing morphology and migrating to the site of infection (Ransohoff and El Khoury, 2015). For example, microglia detect pathogenic agents, remove damaged or apoptotic cells, metabolites, and tissue debris (Färber and Kettenmann, 2005), and defend against pathogen invasion by immune-inflammatory responses (Hickman et al., 2018). Under normal physiological conditions, microglial renewal is completed through self-proliferation when the cellular state is highly branched (Ajami et al., 2007; Torres-Platas et al., 2014), with tertiary and quaternary branching structures and little overlap of intercellular branches. They participate in neurogenesis by establishing neuronal circuits and maintaining the dynamic balance of the neuronal cell pool (Pierre et al., 2017). They release cytokines, such as TNF-α and interferon gamma (IFN-γ), to regulate communication between neurons and other glial cells, and mobilize the activation of other immune cells (e.g., astrocytes) in the brain as a means of removing toxic substances (Sierra et al., 2010; Tremblay et al., 2010; Hansen et al., 2018). They participate in neuronal repair, remodeling, synaptic pruning, and support neuronal survival and differentiation, thus maintaining the homeostasis of the microenvironment within the brain (Eyo and Dailey, 2013). In addition, brain-derived neurotrophic factor (BDNF) signaling promotes synapse formation, which is associated with higher cognitive functions, such as learning and memory (Parkhurst et al., 2013), and participates in the regulatory process of the entire nervous system through the terminal phagocytosis of newly apoptotic neurons in the granular cell layer of the hippocampal dentate gyrus via the protrusions. When the brain microenvironment homeostasis is destroyed, microglial cells will actively respond through a change in their morphology, which includes enlarged cell bodies, shorter protrudes, and round or rod-shaped cell morphology (Choi et al., 2012).

Microglia are traditionally classified according to their functions and features in different states: the M1 phenotype, which promotes inflammation, and the M2 phenotype, which inhibits inflammation (Guo et al., 2022). However, this classification is inconsistent with the wide range of states and functions of microglia in development, plasticity, aging, and disease, which have been elucidated in recent years. Although this term is still widely used, we should

strictly avoid using M1 and M2 to classify microglia and name them using more detailed tools to study their functional state. Current studies suggest that microglia exist in different, dynamic, and multidimensional states and switch between active states by responding to different factors and various microenvironmental changes (Hanisch, 2013; Orihuela et al., 2016; Paolicelli et al., 2022). It is believed that microglia are mainly neurotoxic and neuroprotective in neurodegenerative diseases (Nizami et al., 2019; Xu et al., 2023; **Figure 2**).

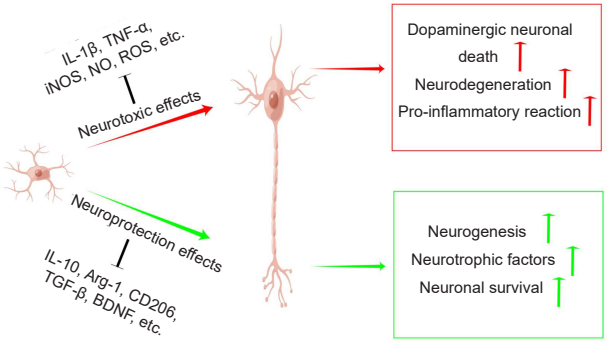

Figure 2 | The role of microglia in different cellular states.
Microglia responding to changes in the brain microenvironment can manifest as different cellular states. Microglia in a neurotoxic state amplify neuroinflammation by secreting pro-inflammatory cytokines, such as IL-1β, TNF-α, iNOS, and chemokines, inducing neuronal death, causing neurodegeneration, and exacerbating disease progression. The neuroprotective state of microglia results in the release of anti-inflammatory mediators and neurotrophic factors, such as IL-10 and Arg-1, to reduce inflammation, protect neurons, and promote neuronal repair. Created with Figdraw. Arg-1: Arginine 1; BDNF: brain-derived neurotrophic factor; IL: interleukin; iNOS: inducible nitric oxide synthase; NO: nitric oxide; ROS: reactive oxygen species; TGF-β: transforming growth factor factor-beta; TNF-α: tumor necrosis factor-alpha.

In neurodegenerative diseases, microglia respond to senescence and the surrounding environmental stimuli (e.g., lipopolysaccharide, IFN-γ, and cellular/bacterial debris) and exert neurotoxic effects that promote the development and progression of neuroinflammation by releasing multiple pro-inflammatory factors and cytokines, leading to neuronal damage and accelerating the progression of neurodegenerative diseases (Wilms et al., 2003; Colonna and Butovsky, 2017). As the brain ages, endogenous stimuli (aggregated α-synuclein (α-syn), deposited amyloid-β (Aβ), and tau oligomers) may lead to an excessive inflammatory response in neurotoxic microglia, resulting in irreversible neuronal damage (Tang and Le, 2016). In addition, microglia in a neurotoxic state amplify BBB damage by releasing pro-inflammatory cytokines and chemokines, such as TNF-α, inducible NOS (iNOS), and CCL-5, which in turn promote the conversion of astrocytes to type A1 (Liddelow et al., 2017; Wan et al., 2022). After BBB injury, chemokines released from microglia induce infiltration of peripheral circulating immune cells into the brain, which further amplifies the inflammatory response, leading to tissue damage and apoptosis (Kim et al., 2022). In contrast, neuroprotective microglia play a role in the allergic response, parasite clearance, inflammation suppression, tissue remodeling, immunomodulation, and tumor promotion by releasing anti-inflammatory cytokines and trophic factors, which support neuronal survival (Sica and Mantovani, 2012; Jetten et al., 2014; Tang and Le, 2016). In addition to releasing inflammatory cytokines and chemokines, microglia can maintain neuronal microenvironmental homeostasis through phagocytosis and the removal of potentially threatening substances (Cai et al., 2022). Microglial phagocytosis plays a vital role in neurodegenerative diseases. Studies have shown that when microglial phagocytosis is impaired, it leads to the abnormal accumulation of Aβ proteins in AD, promotes the accumulation of Huntington's protein in HD, and causes an abnormal increase in α-syn in PD (Harry, 2013; Fu et al., 2014; Jung and Chung, 2018). These disease-specific protein aggregates lead to neuronal death, exacerbating the disease process (Harry, 2013; Fu et al., 2014; Jung and Chung, 2018). Studies have shown that the expression of ATP-binding cassette transporter (ABC) is closely linked to microglial phagocytosis, a class of ATP-driven pumps that, under normal physiological conditions, are widely distributed in the cytoplasmic membranes of organs such as the brain, liver, small intestine, and kidney to remove natural toxicants and metabolic wastes from body (Mahringer and Fricker, 2016; Sakae et al., 2016). ABCA7 belongs to the A subfamily of ABC transporter proteins and is involved in the efflux of cellular cholesterol and phospholipids in various cell types (Li et al., 2015). Notably, there is growing evidence that ABCA7 plays a potential role in the pathogenesis of neurodegenerative diseases such as late-onset AD (Aikawa et al., 2018; Dehghan et al., 2022). ABCA7 deficiency reduces the phagocytic capacity of macrophages and impairs the cytokine response of natural killer T cells (Tanaka et al., 2010; Nowyhed et al., 2017; Aikawa et al., 2019). Studies have shown that ABCA7 is highly expressed in microglia (Kim et al., 2006), which act as phagocytic cells, and that it may contribute to disease development by affecting the phagocytic function of microglia, exacerbating the accumulation of abnormal proteins (e.g., Aβ), and accelerating neuronal damage (Sakae et al., 2016). In conclusion, ABC transporter proteins can influence the progression of neurodegenerative diseases by affecting the phagocytosis of macrophages.

Neurotoxic microglial-mediated neuroinflammation is a common feature of several neurodegenerative diseases. However, neuroprotective microglia exert neuroprotective effects by releasing anti-inflammatory mediators and alleviate neurotoxic-induced inflammatory effects (Wilms et al., 2003; Jetten et al., 2014; Tang and Le, 2016). Therefore, reversing microglial-mediated neuroinflammation and promoting their neuroprotective effects can slow down the development of neurodegeneration and reduce neuronal damage. Microglia are a double-edged sword that play an essential role in neurodegenerative diseases.

Heterogeneity of Microglia in Different Neurodegenerative Diseases

AD

AD is a chronic neurodegenerative disease and the most common cause of human dementia worldwide (Holtzman et al., 2011; Serrano-Pozo et al., 2011). AD patients experience memory loss and difficulties in thinking, language, and problem-solving skills. Recent data suggests that the prevalence of dementia will double in Europe and triple globally by 2050 (Scheltens et al., 2021).

Neuropathological features of AD include deposition of extracellular Aβ plaques and α-syn, activation of astrocytes/microglia, hyperphosphorylated tau protein aggregates within neurons, neuroinflammation, and neuronal cell death (Fakhoury, 2018; Shi et al., 2019; Tan et al., 2021). An accurate diagnosis of the disease in the early stages of AD is the key to treatment, and pharmacological interventions can slow the disease process and reduce morbidity (Bjerke and Engelborghs, 2018; Khan et al., 2020). The only conclusive way to diagnose AD is to perform a brain autopsy on the patient's brain tissue and determine whether the subject has AD or any other form of dementia (Khan et al., 2020). However, the lack of feasibility of this approach and the fact that the etiology of most AD patients remains unknown beyond the genetic differences poses a significant challenge in slowing or treating the disease (Khan et al., 2020). Therefore, it is necessary to understand the pathophysiology of AD, grasp the causes of AD, rapidly diagnose AD, and identify possible therapeutic targets that can be used to prevent or treat the disease to reduce its prevalence and incidence globally.

AD is a complex and heterogeneous disease, and its pathogenesis is closely related to age, genetics, and environmental factors (Calderon-Garcidueñas and Duyckaerts, 2017; Scheltens et al., 2021). A study assessed the ability of bone marrow-derived macrophages in ABCA7-bearing mice to take up oligomeric Aβ and demonstrated that ABCA7 deficiency affects the clearance of Aβ by microglia (Lee and Landreth, 2010; Li et al., 2015), suggesting that microglia play a vital role in the phagocytic clearance of Aβ in the brain. However, the balance between Aβ production and clearance determines the Aβ load in the AD brain, and excessive Aβ accumulation triggers neuroinflammation (Mawuenyega et al., 2010; Colombini et al., 2022). However, ageing further increases the deposition of Aβ and tau, which exacerbates neuroinflammation and decreases neuronal survival, promoting cognitive decline and accelerating the disease process (Mawuenyega et al., 2010; Colombini et al., 2022). Studies have shown that as the brain ages, microglia in AD patients experience increased levels of DNA damage, accelerated telomere shortening, and a slowing of the cell cycle (Pierce et al., 2017; Sarlus and Heneka, 2017). At the same time, microglia have increased inflammatory activity, impaired phagocytosis, and reduced neuronal protection (Pierce et al., 2017; Sarlus and Heneka, 2017). In addition, mitochondrial dysfunction and excessive oxidative stress are not only important features of brain aging but also contribute to early neuronal changes in AD patients (Venkataraman et al., 2022); the aggregation of Aβ and tau proteins causes redox imbalance and oxidative stress, which accelerates the aggregation of Aβ and tau proteins, forming a vicious circle (Zhao and Zhao, 2013). The vicious circle aggravates the damage to healthy neurons (Zhao and Zhao, 2013). Thus, excessive oxidative stress induced by senescence is involved in the onset and development of AD.

Furthermore, Aβ accumulation and tau pathologically drive neuronal senescence, while specific elimination of aging neurons reduces neurodegeneration (Guerrero et al., 2021). Most importantly, the accumulation of age-related senescent cells in the brain may create an ideal pro-inflammatory environment for AD pathogenesis, in which microglia, astrocytes, and neurons are involved and participate in the development and progression of neuroinflammation through various signaling and injury stress responses (Guerrero et al., 2021). Meanwhile, Aβ-induced microglial activation and the release of inflammatory cytokines lead to neuronal senescence and loss of function (Hu et al., 2019). Therefore, modulating neuroinflammation caused by senescence in AD through targeted therapy may provide new ideas for treating AD.

In the early stages of AD, microglia slow the progression of AD by releasing degradative enzymes to clear Aβ plaques and secrete trophic factors to increase tissue repair and maintain homeostasis in the brain, protecting damaged neurons (Heneka, 2017; Sarlus and Heneka, 2017). However, in the later stages of AD, excessive accumulation of abnormal proteins and increased senescence lead to changes in the homeostasis of the brain microenvironment, prompting microglia to become more sensitive to inflammatory stimuli, which accelerates Aβ plaque formation by secreting

large amounts of inflammatory cytokines (Hu et al., 2021). In addition, microglia exert neurotoxic effects due to changes in their cellular state in response to excessive accumulation of Aβ and the surrounding environment, which not only fails to remove the abnormally accumulated proteins but also further induces Aβ production and promotes the activation of many inflammatory pathways (e.g., NOD-like receptor family and pyrin structural domain 3-containing (NLRP3) inflammatory vesicles), increasing the release of pro-inflammatory cytokines and accelerating neurodegeneration (Venegas et al., 2017; Mata-Martínez et al., 2022; Merighi et al., 2022). The accumulation of hyperphosphorylated tau protein in neurons is a feature of AD pathology. Tau promotes microglia senescence, leading to a reduction in their phagocytic function (Brelstaff et al., 2021; Ju and Tam, 2022). Microglia secretes tau protein, which aggravates neuronal damage, and also contributes to the senescence of neighboring microglia, creating a vicious circle and accelerating AD-related pathology (Brelstaff et al., 2021; Ju and Tam, 2022). Notably, in late-onset AD, the ABCA7 gene variant, as a susceptibility gene, is not only involved in regulating microglia dysfunction during brain aging but also in maintaining the immune system homeostasis *in vivo*, and is involved in the pathogenesis of AD through the inflammatory pathway (Aikawa et al., 2019). By regulating the phagocytosis of Aβ by microglia and thus interfering with normal endosomal-lysosomal transport, it leads to the abnormal accumulation of Aβ in the microglia and accelerates APP processing, thereby exacerbating neuronal damage and promoting AD progression (Aikawa et al., 2018).

In addition, as the condition worsens, the response to persistent inflammation and overexposure to oxidation can also promote microglia to switch to the neurotoxic state, leading to neuroinflammation, oxidative stress, iron overload, and neurotoxicity, and reducing the release of neurotrophic factors, leading to a reduction in the average neuronal number and function, promoting the progression of AD (Li et al., 2018; Merighi et al., 2022). Thus, microglia have a bidirectional role in the development and progression of AD. Therefore, promoting the change of microglia from a neurotoxic to a neuroprotective state through drugs or other technical means and regulating the balance of their protective effect on neurons and the clearance of Aβ and tau may effectively reduce the neuroinflammation of microglia in AD, alleviate the pathogenesis of AD, and provide a potential reference for the treatment of AD.

HD

HD is an autosomal dominant neurodegenerative disease that affects approximately 5–10 per 100,000 people, with onset primarily in adulthood. Its clinical manifestations include impaired motor and cognitive function, loss of self and spatial awareness, increased depression, dementia, and anxiety, behavioral dysfunction, brain atrophy, weight loss, and a shortened life span (Georgiou-Karistianis et al., 2013; Labbadia and Morimoto, 2013). At the molecular level, HD is a disease caused by the amplification of CAG repeats in the huntingtin protein gene, leading to the amplification of the polyglutamine region in exon 1. When the number of CAG repeats is expanded from the normal population range (on average between 16 and 20 repeats) to > 35 repeats, the translated polyglutamine-containing mutant huntingtin (mHTT) protein forms inclusion bodies that subsequently harms various types of brain cells (e.g., neurons, astrocytes, and microglia), leading to alterations in transcription, axonal transport, mitochondrial function, vesicular transport, inflammation, and oxidative stress, which in turn promote disease progression (Shin et al., 2005; La Spada et al., 2011; Munoz-Sanjuan and Bates, 2011). The main mechanisms involved in the development of HD are impaired vesicular transport of brain-derived neurotrophic factor (Gauthier et al., 2004), excitotoxicity induced by excessive activation of N-methyl-D-aspartate receptors (Fan and Raymond, 2007), transcriptional dysregulation (Steffan et al., 2000; Hodges et al., 2006), altered protein deposition (Soares et al., 2019), mitochondrial dysfunction (Zheng et al., 2018), and cell-autonomous and non-cell-autonomous mechanisms (Creus-Muncunill and Ehrlich, 2019).

Studies have shown that microglial over-reactivity is a crucial feature of HD pathology and that neuroinflammation characterized by the presence of reactive microglia, astrocytes, and inflammatory factors in the brain is observed in HD patients before the appearance of motor and cognitive impairment symptoms (Donley et al., 2021; Saba et al., 2022). Moreover, neurons expressing mHTT initiate a local response in microglia, leading to an increase in their number and a change in their states (Ellrichmann et al., 2013; Yang et al., 2017). In response to the accumulation of increased mHTT, microglia are hyperactivated, reversing the neuroprotective effect by secreting inflammatory cytokines, exacerbating neuroinflammation, and accelerating the disease process in HD (Ellrichmann et al., 2013; Yang et al., 2017). A study has also shown that inflammatory vesicles may be critical regulators mediating neuroinflammation in neurodegenerative diseases (Heneka et al., 2013). Inflammatory vesicles are essential regulators of the innate immune response and are responsible for the maturation of inflammatory cytokines and cysteine protease-1 during neuroinflammation; NLRP3 inflammatory vesicles are particularly associated with senescence and are activated in response to different molecular patterns associated with injury, leading to chronic low-grade inflammation (Feng et al., 2021; Holbrook et al., 2021). Overactivated NLRP3 inflammatory vesicles are involved in the pathogenesis of several neurodegenerative diseases associated with aging (e.g., HD and PD) (Feng et al., 2021; Holbrook et al., 2021). Furthermore, NLRP3 inflammasomes interact with mitochondrial autophagy. When activation of NLRP3 inflammatory vesicles in microglia are increased, it reduces autophagy and promotes neurotoxicity, accelerating neuronal damage (Guo et al., 2015; Wu et al., 2021). Therefore, the activation of inflammasomes needs to be strictly controlled, and disease progression needs to be slowed down by attenuating NLRP3 inflammasome signaling (Guo et al., 2015; Guan and Han, 2020). In the early stages of HD, microglia become more significant and have shorter protrusions; at this point, they are in a neuroprotective state, reducing the accumulation of mHTT in neurons by increasing their consumption (Milnerwood and Raymond, 2010; Kraft et al., 2012; Crapser et al., 2020). In addition, they release anti-inflammatory cytokines and neurotrophic factors (TGF-β, CD206, arginine-1 (Arg-1), and BDNF), which protect damaged neurons and increase neuronal survival; these neuroprotective effects slow down the progression of the disease (Milnerwood and Raymond, 2010; Kraft et al., 2012; Crapser et al., 2020). However, as the disease progresses, rapidly proliferating microglia are observed near mHTT-expressing neurons (Kraft et al., 2012), which exhibit a neurotoxic state by responding to aging, changes in the brain microenvironment, and misfolded mHTT. In addition to aberrant activation of nuclear factor (NF)-κB-p65, activated NLRP3 in microglia promotes the release of pro-inflammatory cytokines and chemokines (IL- 1β, IL-6, TNF-α, and CCL-5), exerting neurotoxic effects, accelerating neuronal damage, and promoting disease progression (Hsiao et al., 2013; Crotti and Glass, 2015; Siew et al., 2019). Thus, microglia exhibit equally neurotoxic and neuroprotective functions in HD, and by regulating the imbalance in the ratio of neuroprotective to neurotoxic microglia, the neurotoxic effects may be reduced. In addition, promoting mitochondrial autophagy and enhancing the clearance of damaged mitochondria can reduce the accumulation of hypoxia-induced ROS, further attenuating the activation of NLRP3 inflammatory vesicles in microglia and neuroinflammation, increasing the protective effect on neurons, and slowing down the disease process (Han et al., 2019, 2021).

The slow progression of HD and the lack of effective treatments impose a heavy economic burden on families and society (van Duijn et al., 2014). Despite the enormous amount of human and material resources spent to develop therapeutic interventions, there are still no curative or palliative drugs for this devastating disease. Therefore, further research into the pathogenesis of HD and an accurate and sensitive assessment of HD progression by defining appropriate biomarkers are needed to find appropriate treatments (Weir et al., 2011; Byrne and Wild, 2016). Promoting the transition of microglia from a neurotoxic state to a neuroprotective state may alleviate disease progression in HD by intervening in neuroinflammation (Saba et al., 2022). Thus, neuroinflammation may become a new target for HD therapeutic strategies, providing new research directions for treating HD.

PD

PD is an irreversible cognitive and motor disorder caused by structural changes or loss of function of neurons in the body (Tolosa et al., 2006). Its main pathological features are loss of the functional mitochondrial complex I of dopamine (DA) neurons in the substantia nigra pars compacta of the midbrain, accumulation of abnormal proteins, such as α-syn, in Lewy vesicles, and inflammatory responses caused by overreactive glial cell proliferation (Liu et al., 2022). The lack of nigrostriatal-striatal DA neurons leads to the primary motor symptoms of PD, such as tonicity, resting tremor, slow movement, rigidity, and gait disturbances (Mendonça et al., 2017). It is also accompanied by some non-motor symptoms, such as olfactory disturbances, cognitive impairment, psychiatric symptoms, sleep disturbances, autonomic disorders, pain, and fatigue (Kalia and Lang, 2015). Epidemiological studies have shown that PD affects 7–10 million people worldwide, with a prevalence of approximately 1% at the age of 60 years, while the prevalence rises to 4% over the age of 60 years (Bloem et al., 2021). PD not only poses a serious threat to the health of the elderly population, it also imposes a heavy economic burden on their families and society (GBD 2016 Parkinson's Disease Collaborators, 2018). Therefore, how to effectively treat PD has become an urgent problem to be solved.

Various mechanisms have been proposed to regulate the development of PD and neuronal degeneration, including free radical formation (Phaniendra et al., 2015), oxidative stress (Grünblatt et al., 2001), mitochondrial dysfunction (Tufi et al., 2014), excitotoxicity (Mironova et al., 2018), calcium overload (Hirsch et al., 2013), nutrient factor deficiency (Decressac et al., 2011), inflammatory processes (Przedborski, 2010), genetic factors (Deng et al., 2018), environmental influences (Di Monte, 2003), toxic effects of nitric oxide, and cell apoptosis (Bourgognon et al., 2021). Furthermore, senescence plays a vital role in the progression of PD (Collier et al., 2011). During the development of PD, the body experiences reduced proteasome activity, impaired autophagy, and oxidative phosphorylation. Most importantly, mitochondria in DA neurons are damaged with increased oxidative stress, leading to mitochondrial dysfunction, which in turn causes neuronal atrophy and death, and aggravates the PD process (Collier et al., 2017; Theurey and Pizzo, 2018; González-Rodríguez et al., 2021). In addition, senescence causes chronic inflammation in the body, producing SASP, which affects the active state of microglia; this plays a vital role in the neurodegenerative process of PD by mediating neuroinflammatory responses to alter the surrounding stable microenvironment (McGeer et al., 1988; Qin et al., 2021).

However, in PD, low levels of inflammation due to senescence has a positive effect on the overall cellular state by initiating immune defenses to clear harmful substances. However, long-term chronic inflammation leads to a breakdown of this beneficial defense mechanism, and acute systemic inflammation has also been widely shown to affect microglial states (Cunningham et al., 2005; Shemer et al., 2020). Microglia in damaged areas of the PD brain respond to the inflammatory environment by exhibiting a neurotoxic state with the high production of inflammatory factors, including IL-1β, TNF-α, iNOS, nitric oxide (NO), and ROS (Martinez and Gordon,

2014). Among them, TNF-α is the earliest and most crucial inflammatory mediator during the inflammatory response, which activates neutrophils and lymphocytes, and rapidly leads to tissue damage (Pinci et al., 2020). IL-6 and IL-1β promote inflammation and tissue fibrosis (Weber et al., 2010). Overexpression of iNOS enables the release of NO active factors, which further amplifies the inflammatory response in PD leading to the degeneration and necrosis of DA neurons, which in turn leads to degeneration of the nigrostriatal dopaminergic pathway and causes neurodegeneration. In addition, iNOS promotes cytokine and chemokine-induced toxicity and inflammation leading to oxidative stress, which promotes the degeneration of DA neurons. In turn, this promotes neurodegeneration, exacerbates motor deficits in PD, and amplifies extensive damage to adjacent neurons (Brown and Neher, 2014), leading to a vicious circle between dying neurons and neuroinflammation, exacerbating PD progression (Depino et al., 2003; McGeer et al., 2003; García-Domínguez et al., 2018; Badanjak et al., 2021). Damaged DA neurons stimulate microglia, leading to a positive feedback loop of microglia state changes and DA neuron death (Glass et al., 2010).

Neuroprotective microglia promote neuronal repair by taking up glutamate (Byrnes et al., 2009), removing dead cell debris and abnormally accumulated proteins (Diaz-Aparicio et al., 2016), promoting extracellular matrix reconstruction and tissue repair, improving immune regulation, and supporting neuronal survival through neurotrophic factors. However, in PD, neurodegeneration is exacerbated by an imbalance in the ratio of neurotoxic microglia to neuroprotective microglia, resulting in the inadequate protection of neurons (Tang et al., 2014). The conversion of microglia from a neurotoxic to a neuroprotective state is promoted by activating pathways such as peroxisome proliferator-activated receptor γ (PPARγ) and mitogen-activated protein kinase (MAPK), increasing the number of neuroprotective microglia in PD, expanding the repair effect on DA neurons, and alleviating motor and non-motor symptoms in PD (Zhang et al., 2018; Jiang et al., 2020).

The imbalance in the ratio of neurotoxic microglia to neuroprotective microglia in PD results in the presence of high levels of inflammatory factors and ROS in the brain, which leads to a disruption in brain homeostasis and accelerates breakdown of the BBB (Perry et al., 2010). In addition, the inflammatory response of DA neurons is aggravated by the increased phagocytosis and metabolic disorders that exacerbate the inflammatory environment (Mantovani et al., 2004). In conclusion, regulating the balance of microglia in the PD brain by promoting the interconversion of different microglia from a neurotoxic to a neuroprotective state has a promising therapeutic future in treating PD (Hu et al., 2015). However, specific mechanisms regulating the transition of microglia from a neurotoxic to a neuroprotective state need further investigation.

In summary, although the activation of microglia in different neurodegenerative diseases is influenced by various factors, microglia undergo corresponding changes in their states by responding to alterations in the brain microenvironment as aging progresses, further affecting the function of microglia, transforming them from neuroprotective to neurotoxic, and exacerbating neuronal apoptosis and neuroinflammation by promoting disease progression (**Figure 3**). However, regulating the microglial states and alleviating the imbalance of microglia in different states can improve neuroinflammation, thus slowing down the disease progression.

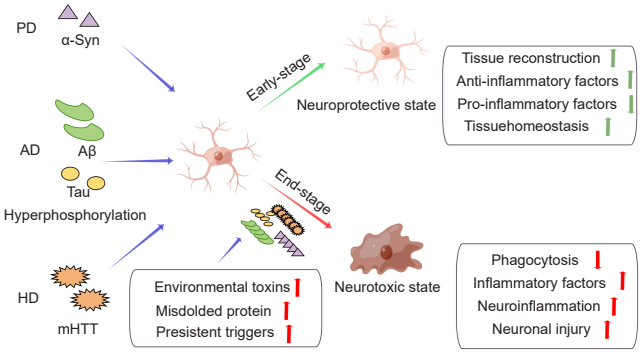

Figure 3 | **The role of microglia in different neurodegenerative diseases.**
The state of microglia is closely associated with aggregated misfolded proteins that are seen in various neurodegenerative diseases, including AD, HD, and PD. Aggregated α-syn, Aβ/tau oligomers, and mHTT released from neurons into the extracellular space can directly induce the transition of microglia to a neurotoxic state. During the disease onset phase, microglia in the neuroprotective state primarily phagocytose cellular debris, promote tissue reconstruction, and produce anti-inflammatory factors to suppress the pro-inflammatory response and maintain tissue homeostasis. However, due to endogenous stimuli and the persistence of environmental toxins, microglia exhibit neurotoxic effects, and their phagocytosis is reduced. Furthermore, inflammatory factors that produce neuroinflammation are released, resulting in irreversible neuronal loss and disease onset. Created with Figdraw. AD: Alzheimer's disease; Aβ: amyloid-β; α-syn: α-synuclein; HD: Huntington's disease; mHTT: mutant huntingtin; PD: Parkinson's disease.

Potential Drugs Targeting Microglia for the Treatment of Neurodegenerative Diseases

The critical role of the functional state of microglia in maintaining homeostasis in the brain microenvironment and in influencing the course of neurodegenerative diseases has been summarized previously. It has now been shown that targeting the functional state of microglia can be a potential target for treating neurodegenerative diseases (Hu et al., 2015; Prinz et al., 2019). Current studies have revealed that various drugs can target and regulate the functional state of microglia (**Table 1**). In a mouse model of AD, treatment with rutin and curcumin inhibited NF-κB pathway activity and reduced glial cell proliferation, inhibited tau aggregation and its induced cytotoxicity, reduced the production of pro-inflammatory cytokines, and promoted the production of anti-inflammatory mediators and neurotrophic factors, which down-regulated neuroinflammation and improved cognitive function in AD mice (Dairam et al., 2008; Zhang et al., 2019; Sun et al., 2021). In HD, ellagic acid and vanillic acid inhibited microglia overreaction by targeting the IKK-NF-κB signaling pathway, thereby reducing neuroinflammation and oxidative stress and improving motor and cognitive function (Bains et al., 2022). In PD, inhibition of TLR4 and MAPK inflammatory signaling through polysialic and pyrazolo [3,4-d] pyrimidine (KKC080106) modulated microglia state changes and improved inflammatory DA neurodegeneration; therefore, they may be candidates for the prevention of PD and neurodegenerative diseases (Liao et al., 2021; Thiesler et al., 2021; Lee et al., 2022). Overall, targeted modulation of microglia has yielded remarkable results for the treatment of neurodegenerative diseases, and the development of drugs based on this target is expected to be an effective way to regulate the level of inflammation in the brain and restore homeostasis in the brain microenvironment.

Table 1 | **Drugs targeting microglia for the treatment of neurodegenerative diseases**

Drug	Disease	Targer	Function
Curcumin Rutin	Alzheimer's disease	NF-κB	Inhibited NF-κB activity, tau aggregation, and induced cytotoxicity, reduced the proliferation of pro-inflammatory cytokines and glial cells, promoted the production of anti-inflammatory mediators and neurotrophic factors, down-regulated neuroinflammation, and improved the cognitive function of Alzheimer's disease mice.
Ellagic acid Vanillic acid	Huntington's disease	IKK-NF-κB	Inhibited microglia overreaction, thereby reducing neuroinflammation and oxidative stress, and improving motor and cognitive function.
Polysialic	Parkinson's disease	TLR4	Enhanced synaptic plasticity, modulated microglia activation, attenuated inflammatory cytokine release, and improved inflammatory dopamine neurodegeneration.
KKC080106	Parkinson's disease	MAPK	Blocked microglial activation, inhibitd the release of inflammatory factors, and inhibited IκB and P38 MAPK in MPTP mice.

IKK: Inhibitor of κB kinase; IκB: inhibitor of κB; MAPK: mitogen-activated protein kinase; MPTP: mitochondrial permeability transition pore; NF-κB: nuclear factor κB; TLR: Toll-like receptor.

Conclusion

In neurodegenerative diseases, microglia play an important role during aging. On the one hand, microglia remove antigenic substances via phagocytosis of damaged cellular debris. On the other hand, microglia, in response to aging and chronic inflammation, can release cytotoxic factors that aggravate neuronal damage and promote the progression of neurodegenerative diseases. Since microglia have dual effects, studying the mechanism of microglial action in neurodegenerative diseases, regulating the transformation of microglial states in response to changes in the surrounding environment, and limiting their effects on neuronal damage may help to slow down the disease process and improve the therapeutic effect. Thus, microglia are expected to provide a target for new therapeutic strategies in treating neurodegenerative diseases and new ideas for screening and developing potential drug candidates. However, the mechanisms of the transformation of microglial states remain to be further investigated. To elucidate the mechanisms of microglia states transformation, it is possible to reverse the neuroinflammation caused by microglia in a neurotoxic state, regulate the inflammatory reaction, and enhance the protective effect on neurons response to aging and disease, then alleviate the diseases development, further improve of the life quality of patients.

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