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NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - REVIEW ARTICLE

Microglia and Parkinson's disease: footprints to pathology

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Abstract
Parkinson's disease (PD) is a neurodegenerative disease associated with motor deficiency and rigidity. The genetic risks of the disease is reported to be between 5 and 10% depending on the background of the population. While PD is not considered an immune-mediated disease, amounting evidence in recent years suggests a major role of inflammation in the progression of PD. Markers of inflammation can be found around the regions of risk and adjacent to the appearance of Lewy bodies within the basal ganglia and the substantia nigra (SN) that are associated with PD pathology. Microglia, an important type of brain cell, has been reported to play a major role in mediating neuroinflammation and in PD disease pathology. This review aims to point out the potential role of microglia in disease progression and suggest that the interaction of microglia with the dopaminergic neurons may also facilitate the specificity of the disease in brain regions affected by PD.

Keywords Parkinson's disease · Microglia · Inflammation · Neurotoxicity · Therapy

Introduction

Microglia are known as the resident immune cells of the brain originating from the yolk sac and derived from myeloid progenitors at an early embryonic stage (Tay et al. 2017). In health, microglial cells play a protective role through immune surveillance and removal of cell debris. Homeostatic microglial cells appear morphologically uniform; however, their physiological responses are heterogeneous, possibly dependent on their local environment and ongoing neuronal activity (Li et al. 2012; Clark et al. 2015).

Homeostatic microglial cells contribute to brain development by eliminating the apoptotic remains of excess newborn neurons and enhancing neurogenesis (Peri and Nüsslein-Volhard 2008; Shigemoto-Mogami et al. 2014; Tay et al. 2017; Lecours et al. 2018). In a healthy adult brain, microglial cells contribute to the refinement of synapses, and the activity-dependent wiring of neural circuits, which requires microglia-mediated synaptic pruning (Wake et al. 2009; Li et al. 2012; Clark et al. 2015). Furthermore, microglia-specific ablation of brain-derived neurotrophic factor (BDNF) hinders the formation of dendritic spines during motor learning in vivo (Parkhurst et al. 2013). Upon injury or infection, and even chronic psychological stress, microglial cells undergo various functional and morphological changes often designated as microglial "activation" or "reactivity" (McGeer et al. 1988; Nayak et al. 2014; Tay et al. 2017).

Microglial cells are described in different neurodegenerative diseases. Their activation levels are directly linked to the site of pathology (Hickman et al. 2018). Changes in microglial cell density and morphology profoundly impact their functions (Perry et al. 2010; Wolf et al. 2017; Bachiller et al. 2018). Nevertheless, their exact role in the pathology remains unclear. Several papers refer to an increase in different microglia-related cytokines in areas of pathology, and different pathways have been suggested to play a role in neurotoxicity. It has been suggested that microglia cell activity changes during neurodegenerative diseases, such as Alzheimer's disease, and results in impaired and neurotoxic phenotype (Keren-Shaul et al. 2017). Furthermore, activated microglia cells have been suggested to orchestrate neuroinflammation and migration of peripheral immune cells (Schwartz et al. 2013). In this review, we focus on the role of microglia during the progression of Parkinson's disease (PD).

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Activation of microglia in Parkinson's disease

Parkinson's disease is a neurodegenerative disease associated with a loss of dopaminergic neurons and impaired motor activity (Dickson 2012). Pathological phenotypes of PD are associated with the appearance of abnormal protein aggregations, called Lewy bodies, within the dopaminergic neurons. It has been suggested that the aggregates consisting of alpha-synuclein (αSyn) spread along the nervous system in six different stages when disease progresses and was found in the autonomic and enteric nervous system with clear evidence in both the central and the peripheral nervous system (Braak et al. 2003; Boeve 2007). Aggregation of αSyn is linked to severe motor impairment and neurodegeneration in the striatum, basal ganglia, and substantia nigra (SN) (Meade et al. 2019). Inflammation has long been proposed as a component of PD (Imamura et al. 2003; Mount et al. 2007; Doorn et al. 2014). Cytokines such as transforming growth factor (TGF)α, TGFβ1, interleukin (IL)-1β, IL-2, IL-4, and IL-6 have been reported to increase in the striatum and in the cerebrospinal fluid of PD patients (Vawter et al. 1996; Nagatsu and Sawada 2005). Moreover, the cerebrospinal fluid of PD patients has been shown to be toxic to DA neurons in vitro due to a high concentration of cytokines (Nagatsu and Sawada 2005). It has been suggested that since microglia are the resident immune cells of the CNS, then they might mediate the inflammatory response in PD (Lecours et al. 2018).

Microglial cells are abundant in the regions of the basal ganglia and SN, and therefore have been previously suggested to be causally linked to the dopaminergic neuron susceptibility to inflammatory mediators (Lawson et al. 1990; Lecours et al. 2018). PD patients stained positively for pro-inflammatory cytokines, such as tumor necrosis factor (TNF)α and interleukin (IL)-6 (Imamura et al. 2003), and reactive microglial cells in the SN in postmortem brain tissue of patients have been reported as early as 1988 (McGeer et al. 1988). Furthermore, an elevation of the leucine-rich-repeat and pyrin-domain-containing 3 (NLRP3) inflammasome has been observed in microglial cells in PD patients' SN section (Gordon et al. 2018). It has been previously reported that an elevation of NLRP3 inflammasome within microglial cells is linked to an increase in the secretion of pro-inflammatory cytokines associated with neurodegeneration (Haque et al. 2020).

It has been suggested that oligomeric αSyn, specifically its fibrillary form (Hoffmann et al. 2016; Fusco et al. 2017; Ferreira and Romero-Ramos 2018), increased TNF-α and interleukin-1β (IL-1β) that may lead to neuronal stress (Reynolds et al. 2008; Boche et al. 2013; Codolo et al. 2013; Ndayisaba et al. 2019). However, it has also been reported that soluble αSyn can stimulate PD gene-impaired microglial cells, leading to an increase in the secretion of IL-6, IL-1 β and nitric oxide (NO) (Trudler et al. 2014). This may suggest that αSyn in different conformation states may play an essential role in the induction of inflammation. Of note, a recent publication has suggested that a loss of normal intracellular activity of αSyn in T cells may induce a neurotoxic profile through modulation of the transcription factor Nurr1. This suggests that a loss of normal intracelular activity of αSyn can attribute to a pro-inflammatory profile in PD (Trudler et al. 2020). The elevation in TNF-α was linked to an induction of the inflammatory response in several neurodegenerative diseases (Ndayisaba et al. 2019). A secretion of TNF-α by microglial cells may induce oligomerization of αSyn that may be a part of a vicious pathogenic cycle of further activation of microglial cells. TNF-α can induce neuronal death through interaction with TNF receptor I (TNFR I) through an activation of caspase 8 and 10 through glutamate excitotoxicity (Dos-Santos-Pereira et al. 2018). Furthermore, another member of the TNF-α family, tumor necrosis factor-related apoptosis-inducing ligand (TNFSF10), was reported to be secreted by microglial cells and to induce neuronal death (Frenkel 2015) (Cantarella et al. 2015).

Positron emission tomography scans of various brain regions of patients diagnosed with idiopathic PD show increased signals of radiotracers binding selectively to inflammatory microglial cells (Gerhard et al. 2006). Interestingly, the presence of activated microglial cells have been found not only in patients with long-lasting disease, but also in patients recently diagnosed, suggesting that microglial cell activation develops at an early stage of the pathology (Gerhard et al. 2006). Furthermore, the appearance of activated microglial cells correlated with decreased DA neuron density, suggesting that activated microglial cells might contribute to ensuing neuronal damage (Ouchi et al. 2005). Microglial cells can produce neurotoxic reactive species such as superoxide and nitric oxide, and these can induce cellular stress, which may promote neuronal loss in PD (Block et al. 2007).

Microglial cells have been reported to express all dopamine receptors (Pocock and Kettenmann 2007). A stimulation of microglial cells by dopamine can result in an increase in ROS production through an elevation of the degrading enzyme monoamine oxidase (MAO) B (Trudler et al. 2014). An activation of microglial cells through CD14 by lipopolysaccharide (LPS) is commonly used to assess their neurotoxic phenotype. LPS-activated microglial cells have been shown to secrete pro-inflammatory cytokines (IL-1α, IL-1β, IL-6, IL-12(p40), TNF-α) in newborn primary cultures, as well as in mice, in vivo. Furthermore, an increase in nitric oxide (NO) and reactive oxidative species (ROS) production has been identified in microglial cells following LPS

stimulation (De Jong et al. 2008; Trudler et al. 2014; Park et al. 2015). A direct injection of LPS to the striatum leads to neuroinflammation, which results in stress to dopaminergic neurons (Liu and Bing 2011). Grouped together with reports regarding microglial cell activation in different PD mouse brain models (Perry 2012), these results suggest the potential role of microglial cell activation in the progression of a PD-like pathology.

Microglial cells have been reported to secrete different complement components and to interact with them (Zabel and Kirsch 2013). It has been suggested that this interaction may attribute to synapsis pruning that is associated with neurodegeneration (Hong et al. 2016; Koenig and Dulla 2018). It has been reported that an increase in complement components was found surrounding Lewy bodies in PD patients suggesting their role in disease pathology (Loeffler et al. 2006).

Of note, an activation of microglial cells may play a role in the clearance of different abnormal amyloid appearances, such as with αSyn, and prevent their propagation across the brain (George et al. 2019). However, a recent publication suggests specific changes in microglial cells upon chronic activation in neurodegenerative amyloidogenic diseases, such as Alzheimer's disease (Keren-Shaul et al. 2017). Those pathological changes might trigger a neurotoxic profile of microglial cells such as a propagation of αSyn in the brain (Xia et al. 2019). Microglial cells may lead to inflammatory events that can promote neurotoxicity to dopaminergic neurons associated with PD (Fig. 1). Notably, a loss of dopaminergic neurons of the basal ganglia and SN is a common denominator of both inherited and sporadic forms of PD (Dickson 2012). Therefore, microglial cells may provide a link between understanding the sporadic forms of PD by learning the mechanisms underlying the genetic forms (Blauwendraat et al. 2020). Nevertheless, it remains to be clarified whether microglial cell activation is the result of DA neuron degeneration or the cause.

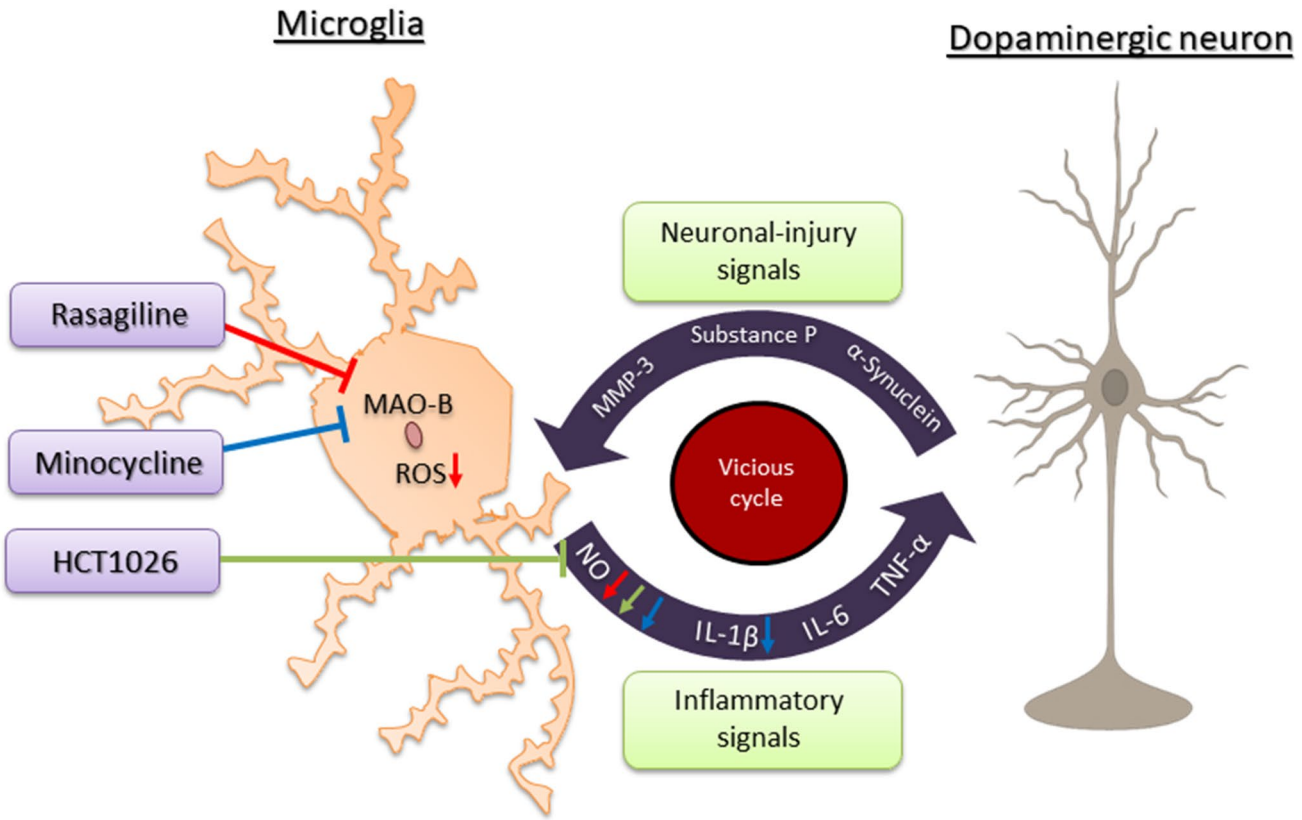

Fig. 1 The effect of therapeutic interventions on the pathologic relationship between microglial cells and dopaminergic neurons in Parkinson's disease. Dopaminergic neurons undergoing degeneration secrete various molecules that cause microglial cell activation, subsequently promoting the secretion of inflammatory molecules that may prompt further neuronal stress. Those interactions may result in a vicious cycle of neuroinflammation. Several FDA-approved drugs (purple) have been shown to positively modulate the inflammatory response of microglial cells. Red arrows indicate the effect of the drug rasagiline in a genetic PD model. Blue arrows indicate the inhibitory effect of the antibiotic minocycline on microglial cell activation in a toxin-based model. Pink arrows indicate the effect of the MPO inhibitor AZD3241. Green arrows indicate the effect of the NSAID compound HCT1026

Mutations associated with PD and their effect on microglial cell activity

It has been suggested that about 5–10% of diseases are the product of highly penetrant (i.e., causal) mutations which have been discovered in several genes of dominant genetic inheritance; such as LRRK2 and the gene encoding αSyn, as well as recessive inheritance, such as Parkin (also known as PARK2), DJ-1 (also known as PARK7) and PINK1 (Singleton et al. 2017). The mutations in the former group are associated with early-onset Parkinsonism and a pathological process that is usually restricted to the brainstem (Puschmann 2013). Recent reports suggest that some of those PD genes may lead to a pro-inflammatory response of microglia as found in PD (Trudler et al. 2015).

Alpha-synuclein is the major component of PD Lewy bodies and, clinically, patients with mutated αSyn have a relatively young age of onset, rapid progression, and high prevalence of dementia, psychiatric, and autonomic disturbances (Dickson 2012). We have recently shown that impairment in αSyn activity within T cells enhances their pro-inflammatory profile (Trudler et al. 2020). Mutations in αSyn have been suggested to lead to abnormal conformation in αSyn resulting in its increased conversion of soluble αSyn into insoluble aggregates that are found in PD (Blauwendraat et al. 2020). Microglial cells that were exposed to extracellular αSyn show increased pro-inflammatory cytokine secretion (Alvarez-Erviti et al. 2011). Microglial cell activation following phagocytosis of aggregated αSyn also enhances dopaminergic neurodegeneration through the production of ROS, in an NADPH oxidase-dependent manner (Zhang et al. 2005). These results suggest that damage to neurons in the substantia nigra may release aggregated αSyn to the substantia nigra, promoting microglial cells to produce pro-inflammatory mediators, thereby further inducing nigral neurodegeneration in PD (Zhang et al. 2005).

High leucine-rich repeat kinase 2 (LRRK1) expression has been discovered in macrophages and monocytes, leading to the speculation of a functional role for LRRK2 in the immune system (Singleton et al. 2017). Microglial cell activation has been shown to trigger LRRK2 expression. LRRK2 inhibition, by shRNA, has been reported to attenuate a microglial cell pro-inflammatory response and reduce TNF-α and NO levels following LPS activation (Moehle et al. 2012). This suggests that LRRK2 plays an important role in mediating pro-inflammatory responses in microglial cells. Taken together, these results suggest that LRRK2 mutations, which are gain-of-function mutations, could change the microglial cells toward a pro-inflammatory phenotype, which then changes the microenvironment of the brain, and thereby trigger and/or enhance the pathogenesis of PD.

The gene PARK7 encodes a small peptidase protein called DJ-1, and mutations in this gene have been reported to be a loss of function (Blauwendraat et al. 2020). Indeed, the loss of DJ-1 function impairs nigrostriatal dopaminergic function (Goldberg et al. 2005). Microglial cells can engulf α-syn, possibly via the TLR4 receptor (Stefanova et al. 2011). Interestingly, the ability of DJ-1 to knock down microglial cells from uptaking and degrading soluble αSyn is diminished (Nash et al. 2017). Dysregulation of glial phagocytosis and degradation have been proposed to play a role in PD pathogenesis, and this is further supported by the fact that microglial cells uptake and remove dopaminergic cell debris in vivo (Tremblay et al. 2019). DJ-1 acts as a multifunctional protein involved in anti-oxidative defense, among other functions. DJ-1-deficient microglial cells have been found to have increased monoamine oxidase (MAO) activity which results in an elevation of intracellular ROS, NO, and pro-inflammatory cytokines, leading to increased dopaminergic neurotoxicity of microglia (Trudler et al. 2014). Furthermore, DJ-1 impaired microglial cells show increased sensitivity to dopamine suggesting that impaired microglia may play a role in site-specific stress in PD (Trudler et al. 2014).

Therapeutic Parkinson's disease approaches affecting microglial cell activity

Currently, there is no effective treatment to cure or to prevent Parkinson's disease progression (Foltynie 2015; Kim et al. 2015). Most of the treatments are focused either on increasing the concentrations of dopamine, such as levodopa (L-Dopa) (Kalilani et al. 2019; Zeuner et al. 2019), or slowing its degradation by an inhibition of MAO-B using FDA-approved drugs such as safinamide and rasagiline (Youdim et al. 2005). The recognition of the importance and contribution of inflammation in PD is increasing (Zeuner et al. 2019). The use of classical anti-inflammatory drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) has been suggested to reduce up to 15% of PD incidence in epidemiology studies, however with a limited effect when used in treatment mode when PD is well defined (Gagne and Power 2010). Nevertheless, there is an increase in reports showing the effects of various, new and existing treatments for PD, on microglial cells' neurotoxic profile (Table 1, Fig. 1).

MAO-B inhibitors, such as rasagiline and safinamide have been shown to reduce the active morphology of microglia and their neurotoxic phenotype (Trudler et al. 2014; Sadeghian et al. 2016). Furthermore, it has been reported that rasagiline, an irreversible MAO-B inhibitor that was developed by Youdim and colleagues, can attenuate DJ-1 impaired microglia and used as a PD-associated microglia model which shows an increase in the production of ROS,

Table 1 PD-related treatments and their effect on microglia activity

Treatment	Activity	Effect on microglia	Experimental model	References	Clinical phase
Rasagiline	Brain-selective monoamine oxidase (MAO) B inhibitor	Reduction of ROS and NO secretion, following dopamine stimulation Reduction of neurotoxic phenotype	N9 cell line—DJ1 deficient	Trudler et al. (2014)	Approved for treatment by the FDA (US Food and Drug Administration 2017)
Minocycline	Antibiotic, tetracycline derivative Penetrates the BBB	Reduction of cells' active morphology Inhibition of IL-1β production Inhibition of NADPH-oxidase enzyme Inhibition of iNOS enzyme	MPTP mice	Wu et al. (2002)	Approved for treatment by the FDA (US Food and Drug Administration 2017)
Levodopa (L-DOPA)	Amino acid, immediate precursor for catecholamines	Inhibition of NO production (at very high concentrations: $IC_{50} = 84.2uM$)	N9 cell line	Chang and Liu (2000)	Approved for treatment by the FDA (US Food and Drug Administration 2017)
		Increased microgliosis Increased TNF-α (following pulsatile but not continuous administration)	6-OHDA-lesioned Sprague–Dawley (SD) rats	Mulas et al. (2016)	
Safinamide	MAO-B and sodium channel blocker	Reduction of cells' active morphology Reduction in MHCII + phenotype	6-OHDA-lesioned SD rats	Sadeghian et al. (2016)	Approved for treatment by the FDA (US Food and Drug Administration 2017)
AZD3241	Myeloperoxidase (MPO) inhibitor	Reduction of cells' active morphology Reduction of ROS production	Clinical trial (phase 2a) on PD patients	Jucaite et al. (2015)	Phase 2: completed (Jucaite et al. 2015)
Nuclear receptor related-1 (Nurr1) agonists	Related to reduction of pro-inflammatory cytokines and neurotoxic factors	Reduction in mRNA expression of pro-inflammatory phenotype (IL-1β, IL-6, TNF-α, iNOS)	Primary microglia from P1 rat brains	Kim et al. (2015)	Some compounds are approved by the FDA for other purposes than PD (Kim et al. 2015)
		Reduction of cells' active morphology	6-OHDA-lesioned SD rats	Kim et al. (2015); Smith et al. (2015)	
Trihexyphenidyl (THP)	Anticholinergic (AC) compound	Increased cells active morphology	Tauopathy mouse model (PS19) SD rats	Huang et al. (2016); Yoshiyama et al. (2012)	Approved for treatment by the FDA (US Food and Drug Administration 2017)
		Increased expression of CD68 (related to phagocytosis promotion) Upregulation of muscarinic M1 receptor (related to phenotypic changes)	SD rats	Huang et al. (2016)	

Table 1 (continued)

Treatment	Activity	Effect on microglia	Experimental model	References	Clinical phase
Ibuprofen	A non-steroidal anti-inflammatory drug (NSAID)	Decreased phagocytosis in activated cells No effect on NO production in activated cells	Co-culture of BV2 microglial cell line with NT2 neuronal cell line	Scheiblich and Bicker (2017)	Approved by the FDA as an analgesic (US Food and Drug Administration 2017)
HCT1026	A NO-donating derivative of flurbiprofen (NSAID)	Reduction of cells' active morphology Reduction of iNOS expression Reduction of oxidative stress	C57BL/6 mice	L'Episcopo et al. (2011)	Flurbiprofen is approved by the FDA for other purposes than PD (US Food and Drug Administration 2017)
Deep brain stimulation (DBS)	Transfer of electrical current to specific areas of the brain through electrode implantation	Reduction of cells' active morphology	Tg-F344-AD rats SD rats	Leplus et al. (2019); Vedam-Mai et al. 2016)	Approved for treatment by the FDA (Center for Devices and Radiological Health 2017)

IL-1b and IL-6 (Trudler et al. 2014). Rasagiline was found to attenuate the microglial cells' neurotoxicity profile to dopaminergic neurons.

Nuclear receptor related-1 (Nurr1) is important for the development of dopaminergic neurons in the midbrain. Genetic deletion of Nurr1 in mice showed a reduction in dopaminergic neurons (Dong et al. 2016). A mutation in Nurr1 was found in PD. Nurr1 agonists show efficacy in a mouse model of PD by attenuating microglial cell activity. Similarly, the use of the antibiotic minocycline showed a similar effect on microglia cell activity, with a successful reduction of oxidative stress and inflammatory cytokine levels (e.g., IL-1β, TNF-α) in a PD model (Wu et al. 2002; Kim et al. 2015; Smith et al. 2015).

The use of anticholinergic compounds (AC), such as trihexyphenidyl (THP), is also commonly used to treat PD. ACs were introduced at the end of the nineteenth century and have been shown to possess a relieving effect on PD motor symptoms, especially on tremors (L'Episcopo et al. 2011; Yoshiyama et al. 2012; Huang et al. 2016; Zeuner et al. 2019; Hong et al. 2019). Acetylcholine has been reported to have an anti-inflammatory effect (Pavlov et al. 2003). Indeed, in several models of PD, THP has been shown to promote CNS neuroinflammation as well as microglial cell activation (Table 1).

Myeloperoxidase (MPO) is a peroxidase expressed in immune cells such as macrophage and microglia and plays a role in increased ROS production as part of a defense against pathogens (Aratani 2018). Its level was reported to elevate following inflammation and to promote tissue damage (Nakazato et al. 2007). It has been reported that MPO levels are elevated in PD (Gellhaar et al. 2017; Posener et al. 2014). MPO inhibitors have been shown to reduce ROS production and cell proliferation in microglia (Jucaite et al. 2015). Currently, MPO inhibitors are in clinical trial in PD and show efficacy in reducing microglial cell activation in patients.

These results suggest the importance of targeting microglia toward the development of efficient PD treatment.

Conclusions

Microglial cells may play a dual role in PD. On one hand, their activation may prevent spreading of oligomeric αSyn along the brain, and, on the other hand, their activation can lead to dopaminergic neuron stress and death. The ability of microglial cells to interact with specific neurons was suggested by the expression of specific receptors on their surface. Interestingly, microglial cells carrying mutations in PD-related genes showed increased sensitivity to dopamine. Furthermore, those microglial cells showed increased activity of dopamine-degrading enzyme MAO B. This may suggest that besides microglia, a diverse neurotoxic effect

may be common between different neurodegenerative diseases, suggesting that there may be a specific effect toward dopaminergic neurons in PD. Understanding the specificity of microglial cells to dopaminergic neuron neurotoxicity might shed light on their role in the etiology of the disease. Furthermore, several therapeutic approaches in PD that show efficacy have an anti-inflammatory effect on microglial cells. Targeting microglial cell activity to reduce their neurotoxicity while preserving their beneficial neuroprotective role might be a key point in developing efficient therapeutic approaches to prevent disease progression in PD and related neurodegenerative diseases.

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