

# Microglia-Mediated Neuroinflammation in Parkinson's Disease

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**Parkinson's disease (PD) is an age-related neurodegenerative disease, and its main pathological feature is the specific reduction of dopamine neurons in the substantia nigra of the mid-brain and  $\alpha$ -synuclein aggregates. However, the specific molecular mechanism of the degeneration of dopamine neurons in the substantia nigra is still not fully understood. Neuroinflammation is involved in the development of PD, and microglia-mediated neuroinflammation plays an important role in the degeneration of dopamine neurons. This article will review the mechanism of microglia-mediated neuroinflammation in the pathological process of PD, and provide new understanding for the molecular mechanism and treatment of PD.**

**Keywords:** Parkinson's Disease; Microglia; Neuroinflammation; Neuronal Transmission; Outcomes

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**T**HE reduction of dopamine neurons in the substantia nigra and the formation of Lewy bodies are the main pathological features of Parkinson's Disease (PD) (1). Clinically, the main symptoms of PD include resting tremor, posture and gait disturbance, and bradykinesia. In addition, PD patients are also accompanied by some non-motor symptoms such as sleep disturbance, fatigue, anxiety, depression, and cognitive decline (2). Studies have found that genetic factors, epigenetic changes, mitochondrial dysfunction, and proteasome system abnormalities are all important factors that promote the occurrence of PD (3, 4). The specific molecular mechanisms of the degeneration of dopamine neurons in the substantia nigra and the formation of Lewy bodies are not fully understood yet. It was found that microglia in the brain of PD patients showed a significant activation state (5, 6), suggesting that neuroin-

flammation plays an essential role in the pathological process of PD. In addition, animal experiments and in vitro experiments have also shown that the neuroinflammatory response mediated by microglia is involved in the development of PD (7).

Microglia account for 5% to 12% of all glial cells, but the specific proportion of each brain region is differentially expressed in different brain regions (8). Microglia have the function of immune defense and maintain homeostasis in the brain and are considered to be the main immune cells in the brain (9). Under normal physiological conditions, microglia are in a quiescent or inactive state, but they can still move through active contraction and expansion movements, thus participating in the regulation of the entire nervous system (10). Under external stimuli and injury conditions, microglia will undergo significant changes in morphology, and quickly move to the injury site, and

then participate in tissue injury repair and disease occurrence and development (11). The activation of microglia will produce a large number of inflammatory factors such as interleukin-1 $\beta$  (IL-1 $\beta$ ), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), IL-6 and IL-12, which in turn lead to an inflammatory response in local tissues (12). This article will review the role of microglia-mediated neuroinflammation in PD, and provide new references for the prevention and treatment of PD.

## Microglia

### Source

Microglia are widely distributed in the central nervous system, and the source of microglia is still controversial. Some believe that microglia originate from mesoderm cells, such as fetal macrophages in the yolk sac or embryonic mesenchymal cells in the pia mater (13). With the development of the embryo, these mesoderm cells in late invasion of the brain to form microglia. In contrast, some believe that microglia originate from neuroectoderm rather than mesoderm. Using macrophage-specific marker protein Ricinus communis agglutinin-1 (RCA-1) and microglia-specific marker protein for immunostaining, and the results suggested that microglia were not derived from pial mesenchymal cells but is derived from the germinal matrix (14). In addition, some believe that microglia originate from monocytes in blood circulation (15). Therefore, more experimental evidence is still needed to elucidate the source of microglia.

### Biological Activity

As immune cells in the brain, microglia are currently considered to have two states, namely M1 type and M2 type, in which M1 type cells are in a pro-inflammatory state, M2 type cells are in an anti-inflammatory state, and M2 type cells are in an anti-inflammatory state (16). In the M1 state, microglia mainly secrete inflammatory factors, such as IL-1 $\beta$ , IL-6, TNF- $\alpha$ , IL-12 and inducible nitric oxide synthase (iNOS), which can cause inflammation in local tissues, leading to tissue damage and cell apoptosis that in turn can cause neurodegeneration. Therefore, in general, these inflammation-related factors serve as marker proteins of M1 microglia. Studies have found that in vitro co-stimulation of primary cultured microglial cells with inflammation-related factors such as bacterial lipopolysaccharides (LPS) and  $\gamma$ -interferon (IFN- $\gamma$ ) can induce microglial cells to form M1 type (17). In the M2 state, microglia mainly secrete growth factors and anti-inflammatory factors, such as transforming growth factor- $\beta$  (TGF- $\beta$ ), IL-10, arginase-1 (Arg-1), resistin-like alpha (RELM $\alpha$ /FIZZ1), polysaccharase (chitinase 3-like protein 3, CHI3L3/YM1) and CD206 and other factors, therefore, these related factors are usually used as marker proteins of M2 microglial cells (18, 19). These M2-related factors have the effect of anti-inflammatory response, which can reduce the inflammatory response of tissue, thereby promoting the repair process of tissue (20). Stimulation of microglial cells with IL-4 in vitro can induce the M2 state of microglial cells (21).

Inflammation and non-inflammation will cause changes in the expression levels of miRNAs in microglial cells, and these miRNAs regulate intracellular inflammation-related signaling

pathways, thereby producing pro-inflammatory or anti-inflammatory effects. For example, the expression level of miR-155 in microglia can be significantly up-regulated under the co-stimulation of inflammatory stimuli such as LPS and IFN- $\gamma$ , while IL-4 stimulation cannot cause the expression of miR-155 in microglia (22, 23). Studies have found that miR-155 can regulate downstream pro-inflammatory signaling pathways such as SOCS1, Creb, and Bcl6, and the above studies suggest that miRNAs also specifically participate in the state regulation of microglia (24, 25). Under normal circumstances, these two states of microglia are in a dynamic balance, but under external injury stimuli or disease states, this balance will be disrupted, causing the body to respond quickly and regulate a homeostasis of microglia. However, it is not clear what form and molecular mechanism of microglia exist in these two states under physiological and pathological conditions.

Many factors can affect the two states of microglia, and under certain conditions, the two states of microglia can change. Kim et al. found that acetylcholine (ACh) could reduce the expression levels of pro-inflammatory factors IL-1 $\beta$  and IL-6 in LPS-induced microglial cell line BV2 cells by Western blot and real-time quantitative PCR (26). Reduce the expression levels of anti-inflammatory factors IL-4 and IL-10 can significantly reduce the activity of inflammation-related pathways JAK2/STAT3 and PI3K/Akt pathways (27). Interestingly, reducing the expression level of the ACh receptor nicotinic acetylcholine receptor  $\alpha 7$  subtype ( $\alpha 7$ nAChR) by virus transfection can significantly reduce the effect of ACh (28). It is suggested that ACh can change the expression level of downstream signaling molecules by combining with its receptor  $\alpha 7$ nAChR, and then promote the transformation of BV2 cells from M1 to M2. In addition,  $\beta$ -Caryophyllene ( $\beta$ -CP) significantly reduces the expression levels of pro-inflammatory factors IL-1 $\beta$  and TNF- $\alpha$  that were induced by LPS through Type II cannabinoid receptor (CB2), and up-regulates the expression of downstream anti-inflammatory related factors IL-10 and Agr-1 that promote the transition of microglial cells from the M1 state to the M2 state (29). These show that the two states of microglia can be transformed under certain conditions. In addition, studies have found that neurological diseases such as Alzheimer's disease (AD) and multiple sclerosis (MS) are accompanied by the occurrence and development of inflammation (30, 31). Therefore, the two different functional states of microglia, either the presence or the transformation provide new therapeutic targets for inflammation-related CNS diseases.

## The Role of Microglia-Mediated Neuroinflammation in PD

### Microglia and the Development of PD

In an inflammatory state, microglia will show a significant activation state, mainly in cell morphology and specific protein expression. On the one hand, the cell body becomes larger, and the processes shorten and thicken; on the other hand, the expression level of the specific marker protein calcium binding protein IBA1 of microglia will be significantly increased. The process of PD is accompanied by the development of inflammatory response. Kübler and coworkers used positron emission tomogra-

phy to find that a large number of microglial cells were activated in the brain of PD patients (32). In the PD animal model induced by neurotoxin MPTP and 6-OHDA, microglia also showed a significant activation state (33), indicating that microglia, as immune cells in the brain, play a pivotal role in the inflammatory response process in the pathological process of PD.

Under the action of external stimuli such as  $\alpha$ -synuclein aggregation or LPS, the microglia in the body will respond quickly and be in a significant activated state, releasing a large number of inflammatory factors, making the injured site in an inflammatory state (34). These inflammatory factors further act on astrocytes. Stimulated astrocytes will also activate and release inflammatory factors, and the inflammatory factors released by microglia and astrocytes act on dopamine neurons at the same time, thereby causing degeneration of dopamine neurons (35). Furthermore, diseased neurons will release a large number of toxic factors to continuously activate microglia, making the body in an obvious inflammatory state, and this cyclical process eventually aggravates the occurrence and development of PD (36). Therefore, the inflammatory response mediated by microglia is closely related to the occurrence and development of PD.

## Mechanism of Action

Peng et al. found that the activation of microglia induced by LPS can significantly enhance the degeneration process of dopamine neuron cell lines induced by the neurotoxin MPP<sup>+</sup>, and increase the expression of JNK and NF- $\kappa$ B in SH-SY5Y cells level (37). In addition, the study also found that activated microglia can enhance the expression levels of apoptosis-related genes such as bax in dopamine neuron cell lines (37). The above results suggest that the activation of microglia induced by drugs in vitro may aggravate the death of dopamine neurons by regulating the activity of specific signaling pathways in dopamine neurons (38). Chronic mild stress stimulation can significantly enhance LPS-induced death of dopamine neurons in PD rats (39). First, chronic unpredictable mild stress can significantly enhance the activation of microglial cells and inflammatory response in the rat brain, and second, it can also significantly increase the activation of inflammasome NLRP3 and the death of dopamine neurons in the substantia nigra. The activation of microglia affects the survival of dopamine neurons by regulating the activity of inflammasomes in the substantia nigra and the inflammatory response (40). Therefore, effectively reducing the degree of activation of microglia can significantly reduce the degenerative process of dopamine neurons in drug-induced PD models.

Nitrated or oxidized  $\alpha$ -synuclein can induce oxidative stress in microglia and promote the formation of M1 activation in microglia (41). MPTP or LPS treatment can induce microglial cells to produce a large number of inflammatory factors, so that microglial cells present an M1-type activated form (42). Meredith et al. found that long-term injection of MPTP and probenecid in mice would cause the number of anti-inflammatory microglia to be significantly more than that of pro-inflammatory microglia in the early stage (43). However, with the gradual injection of drugs, the number of pro-inflammatory microglia the number of glial cells increased

significantly, while the number of anti-inflammatory microglia decreased significantly, indicating that in a specific period of PD, M2 microglial cells dominated, and with the gradual aggravation of the disease, most of the microglial cells released inflammatory factors, so that most of the microglia showed a significant M1 state. Long-term MPTP and probenecid treatment can cause a significant decrease in the expression level of CD206 in microglial cells in the substantia nigra region of mice, indicating the complexity of the two activation types of microglial cells in the process of PD (44, 45). At present, studies have shown that the inflammatory response produced by M1 glial cells can lead to the degenerative process of dopamine neurons (46, 47). However, it is not completely clear that M2 glial cells are involved in the development of PD.

Yu et al. used microglial cell line BV2 cells and dopamine neuron cell line MN9D cells for co-culture, treated with neurotoxin 6-OHDA and microtubule stabilizer EpoB, and used TUNEL apoptosis staining to detect the activity of MN9D cells (48). EpoB can significantly reduce the expression levels of microglial inflammatory factors such as IL-1 $\beta$ , IL-6 and TNF- $\alpha$ , thereby inhibiting the M1 state of microglial cells (49). First, EpoB can significantly reduce the activation of microglial cells in the substantia nigra area caused by 6-OHDA, and second, it can also significantly reduce the neurotoxicity caused by 6-OHDA and substantially enhance the exercise capacity of mice. These findings suggest that EpoB reduces the neurotoxic effect of 6-OHDA on dopamine neurons by inhibiting the transition of microglia to the M1 state (6). Therefore, inhibiting the M1 state of microglia can significantly reduce the neurotoxin-induced dopaminergic degenerative process. Reducing the M1 state of microglia or enhancing M2 microglia during the development of PD is expected to be an effective way to slow down the progress of PD.

The inflammasome NLRP3 plays a critical role in the development of neuroinflammation (50). Abnormal accumulation of metabolites such as  $\beta$ -amyloid and 25-hydroxycholesterol in the body will lead to the activation of NLRP3, which in turn leads to the activation of apoptosis-related enzyme-cysteine-containing aspartic acid hydrolase 1 (caspase-1) and the release of IL-1 $\beta$ , thereby initiating the inflammatory response process (51, 52). Deletion of NLRP3 significantly reduced the activation of microglial cells and the death of dopaminergic neurons in the substantia nigra region of mice induced by MPTP (53). NLRP3-knockout mice showed significantly enhanced exercise capacity after MPTP treatment (54). The activation degree of NLRP3 inflammasome is closely related to the occurrence and development of PD. Kaempferol can reduce the degeneration of dopamine neurons in PD mice by inhibiting the activation of inflammasome NLRP3 (55). Reducing the degree of activation of the NLRP3 inflammasome can significantly reduce the neurotoxin-induced degenerative pathological process of dopamine neurons (56, 57). Therefore, NLRP3 plays a crucial role in the degenerative process of PD. MPTP and ATP treatment can increase the activity of caspase-1 downstream of microglial cells, which can lead to an increase in the expression level of IL-1 $\beta$ , while knockdown of NLRP3 can significantly reduce the increase of caspase-1 activity and IL-1 $\beta$  induced by MPTP and ATP (58). MPTP and ATP stimulation can significantly increase

PI-positive SH-SY5Y cells, but in the co-culture system of SH-SY5Y cells and NLRP3<sup>-/-</sup> microglial cells, MPTP and ATP stimulation did not cause obvious SH-SY5Y cells die (59). Thus, activation of the NLRP3 inflammasome in microglia plays a critical role in the degeneration of dopaminergic neurons.

## Conclusion

The neuroinflammatory response mediated by microglia plays an essential role in the occurrence and development of PD. However, the specific mechanism of the two states of microglia in PD is not completely clear. Microglia showed different activation states under different conditional stimuli, showing M1 type and M2 type in pro-inflammatory and anti-inflammatory states, respectively. The two states of microglia can change under certain conditions. Studies have found that microglia in the two states exhibit two completely different functions of pro-inflammatory and anti-inflammatory. Therefore, it is better

to explore the function of microglia. The mechanism of action of the two states in the occurrence and development of PD and the relationship between the two states help to understand the pathogenesis of PD more profoundly, and provide more possibilities and more accurate methods for the prevention and treatment of PD.

Moreover, the activation of inflammasomes in microglia is also involved in the process of microglia-mediated neuroinflammation. However, there are many types of inflammasomes, and the role of each inflammasome in the process of microglia-mediated inflammatory response is not yet fully understood. Therefore, more clinical and animal experiments are needed to elucidate the specific role of inflammasome in the process of microglial inflammatory response, so as to provide a more in-depth understanding of the function of microglial cell-mediated neuroinflammation in PD. many theoretical bases.■

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