The role of neuroinflammation on the pathogenesis of Parkinson’s disease

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Parkinson’s Disease (PD) is a common neurodegenerative disease characterized by the progressive degeneration of nigrostriatal dopaminergic (DA) neurons. Although the causative factors of PD remain elusive, many studies on PD animal models or humans suggest that glial activation along with neuroinflammatory processes contribute to the initiation or progression of PD. Additionally, several groups have proposed that dysfunction of the blood-brain barrier (BBB) combined with infiltration of peripheral immune cells play important roles in the degeneration of DA neurons. However, these neuroinflammatory events have only been investigated separately, and the issue of whether these phenomena are neuroprotective or neurotoxic remains controversial. We here review the current knowledge regarding the functions of these neuroinflammatory processes in the brain. Finally, we describe therapeutic strategies for the regulation of neuroinflammation with the goal of improving the symptoms of PD. [BMB reports 2010; 43(4): 225-232]

INTRODUCTION

Parkinson’s disease (PD) is a common neurodegenerative disorder characterized by abnormal motor symptoms such as resting tremor, slowness of movement, rigidity and bradykinesia (1). The neuropathological features of PD are progressive death of dopaminergic (DA) neurons in the substantia nigra pars compact (SNpc) and depletion of dopamine in the striatum (STR), which is the site at which these nerve terminals project (2). Along with damage in the SN, eosinophilic inclusions (Lewy bodies) were identified in the brain of PD patients, thus becoming a pathological marker of the disease (3). Nowadays, Lewy bodies and neurites stained with antibodies to ubiquitin, α-synuclein and other biochemical markers are detectable in various brain regions; not only the SN, but also the locus celluleus, raphe, thalamus, amygdala and cerebral cortex (4). These phenomena indicate that PD is involved in multiple neuronal systems in addition to dopamine.

Based on these main neuropathological features, several neurotoxins such as 1-methyl-4phenyl-1,2,3,6-tetrahydropyridine (MPTP), 1-methyl-4-phenylpyridinium (MPP+), 6-hydroxydopamine (6-OHDA), 1,1’-dimehyl-4,4’bipyridinium (paraquat) and rotenone are currently used for the induction of nigrostriatal DA neuronal degeneration (5). Although these toxin-based models of PD have some limitations in exactly reproducing neurotoxic mechanisms in a genetic mutation model (6), the specific features of PD pathogenesis such as neuronal inclusions (7), mitochondrial dysfunction (8), oxidative stress and inflammation (9) are consistently reported. Among them, glial activation-derived oxidative stress and inflammatory molecules play important roles in DA neuronal death in PD patients and animal models (10, 11). These mechanisms are comprised of microglial activation, reactive astrocytes, damaged blood-brain barrier (BBB) and infiltrated peripheral immune cells (Fig. 1, 2). However, these molecular and cellular changes are not specific to PD, since neuroinflammation is also implicated in the development of Alzheimer’s disease (AD), Huntington’s disease (HD), amyotrophic lateral sclerosis (ALS) as well as other neurodegenerative diseases (12). In this review, we describe the evidence for neuroinflammation as a consequence of nigrostriatal DA neuronal degeneration in the brains of PD patients and animal models of PD. Finally, we highlight possible therapeutic targets associated with inflammation that might help to slow down the progression of PD.

Involvement of glial activation in PD

Microglial activation in PD

Microglia are the resident immune cells in the CNS and constitute about 5-20% of all glial cells. They were first identified as a distinct cell entity by Pio del Rio-Hortega (13). The origin of microglia is derived from circulating blood monocytes, which are the progenitors of microglia (14). In the mature healthy brain, resting microglia adopt a ramified morphology...
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Consisting of small cell bodies. Little is known about the function of resting microglia, but they are suggested to function in immune surveillance and host defense by releasing low levels of growth factors (15).

Microglial activation by various stimuli is generally characterized by a gradual change in morphology from a quiescent ramified form (resting state) to an amoeboid form (activated state) (16-19). Several studies have revealed that activated microglia express diverse cell-surface receptors, including the major histocompatibility complex and complement receptors (17, 20) as well as inducible potentially neurotoxic factors (21) that impose chronic inflammation of the brain, leading to neuronal dysfunction and death in the form of neurodegenerative disorders such as PD (22).

In a postmortem analysis of PD patients, activated microglia and reactive human leukocyte antigen-DR (HLA-DR)-positive microglia were found in the SNpc (23, 24). Immunohistochemical studies have shown that numerous activated microglia are present in neurotoxin-treated SNpc in various animal models of PD (25). Consistent with these results, we reported that microglial activation involving the degeneration of DA neurons was observed in the SNpc (26, 27). Several results have suggested that these activated microglia could contribute to nigral DA neurons through oxidative stress and production of

Fig. 1. Various neuroinflammatory processes in the animal model of PD. (A-H) CD11b immunostaining and FITC-linked albumin (FITC-LA) assay showing microglial activation and disrupted BBB in the LPS-induced inflammation model (A-D) and MPTP mouse model (E-H). In PBS-treated control groups (A, B, E, F), ramified microglia and intact BBB FITC-LA were observed. At 3 days after LPS (5 μg/3 μl; C, D) and MPTP (four intraperitoneal injections of 20 mg/Kg; G, H) injection, there was a high amount of activated microglia and FITC-LA leakage in the SN. Colocalization of FITC-LA vessels (green) and CD11b positive cells (red) in the SN treated with PBS (F) or MPTP (H). Two images are merged (yellow). (I-K) Animals receiving intranigral LPS injection were sacrificed at various time points, and tissues were immunostained with each antibody to detect immune cells. The stereological counting results revealed that a number of peripheral immune cells infiltrated into the SN in a time-dependent manner (l). Additionally, colocalization of innate microglia (Iba-1; green) and proinflammatory cytokines (IL-1β and iNOS; red) revealed that innate microglia might contribute to the production of proinflammatory molecules (J, K). Two images are merged (yellow). (L-O) In the MPTP model of PD, immunohistochemical studies revealed that penetration of peripheral immune cells followed different patterns in the SN, compared to LPS-injected SN. The results of stereological counting (data not contain) showed that the majority of infiltrated immune cells were CD3 (I) and CD68 positive (M). Even though a few B cell receptor (N) and MPO-positive cells (O) were detectable in MPTP-treated mice, the total amounts were marginal portions of the total number of immune cells. Dotted lines indicate substantia nigra pars compacta (SNpc) where dopaminergic neurons were degenerated.