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Role of Microglia in Inflammatory Process in Parkinson's Disease

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1. Introduction

1.1 What is Parkinson's disease

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease (AD). PD is characterized by degeneration and cell death in dopaminergic neurons in the substantia nigra pars compacta (SNpc) and loss of their nerve terminals in the striatum (putamen and caudate nucleus), accompanied by the depletion of the neurotransmitter dopamine (DA) in the striatum. This depletion causes motor symptoms, i.e., resting tremor, muscle rigidity, and akinesia. The level of tyrosine hydroxylase (TH), the rate-limiting enzyme of catecholamine (DA, noradrenaline, and adrenaline) synthase in the nigro-striatal region of PD patients is decreased (Nagatsu and Sawada M., 2007).

A small percentage of PD is familial with a hereditary history. However, most cases of PD (approximately 90-95 %) are sporadic without any hereditary history. In 2009, 16 causative genes of familial PD have been identified (Satake et al., 2009), including PARK1 (α -synuclein), PARK2 (*parkin*), PARK4 (α -synuclein), PARK5 (*UCHL-1*), PARK6 (*PINK1*), PARK7 (*DJ-1*), PARK8 (*LRRK2*), and PARK9 (*ATP13A2*). Sporadic PD and some cases of familial PD are characterized by the presence of cytoplasmic inclusions named Lewy bodies, which consist mainly of α -synuclein protein, the product of the PARK1 gene. α -Synuclein is observed not only in PD but also in various neurodegenerative diseases, such as dementia with Lewy bodies (DLB).

Based on their investigation of the distribution of α -synuclein-positive Lewy bodies and Lewy neurites in PD patients, Braak et al. (2003) proposed a hypothesis that the pathological process of PD starts first from the lower brain stem and then spreads to the midbrain, limbic system, and cerebral cortex. α -Synuclein-positive inclusions are observed in the anterior olfactory nucleus, dorsal motor nucleus of vagus nerves, and also in peripheral autonomic neurons including those of the sympathetic ganglia, adrenal medulla, and intestinal Auerbach's plexus. Braak et al. (2003) proposed that symptoms of PD appears when Lewy bodies are formed in dopaminergic neurons in the substantia nigra (SN) .

The neuronal cells overexpressing α -synuclein were reported to directly transfer α -synuclein protein to neighboring normal neuronal stem cells both in cell culture and in transgenic mice; PD-like pathological changes occurred in such stem cells with development of inclusion bodies, lysosomal failure, and apoptotic changes (Desplats et al., 2009). This study could explain the findings that PD patients who had been treated more than ten years prior to death by implantation of human fetal mesencephalic dopaminergic neurons into their striatum had continued to develop PD pathology with loss of dopaminergic neurons and, importantly, the formation of Lewy bodies in the graft cells (Kordower et al. and Li et al., 2008). These findings indicating that α -synuclein pathology may spread throughout the nervous system from one cell to another, like a prion infection, would appear to fit the above hypothesis offered by Braak et al. (Olanow and Prusiner, 2009).

The animal models of PD are produced by several neurotoxins of dopaminergic neurons, e.g., 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), 6-hydroxydopamine (6-OHDA), paraquat, and rotenone (Miller et al., 2009; Nagatsu and Sawada M., 2006). Systemic administration of MPTP produces PD in humans, monkeys, and various animals. MPTP enters into the brain through the blood brain barrier (BBB), is metabolized to 1-methyl-4-phenyl-pyridium ion (MPP⁺) by monoamine oxidase (MAO) B in astrocytes, and is specifically transported into dopaminergic neurons in the SN. In these dopaminergic neurons, MPP⁺ inhibits mitochondrial complex I, depletes ATP, and causes the release of reactive oxygen species (ROS), and apoptotic cell death. Since 6-OHDA does not cross the BBB, direct stereotaxic injection into the nigro-striatum is used to produce hemiparkinsonian animal models. Rotenone and paraquat are non-selective dopaminergic neurotoxins, which are used as a pesticide. Both compounds cause degeneration of dopaminergic neurons, accompanied by mitochondrial dysfunction, when chronically administered to animals. These neurotoxins also inhibit mitochondrial complex I and cause the release of ROS and the depletion of ATP in dopaminergic neurons in the SN, thus triggering cell death.

The pathogenesis of sporadic PD is still uncertain, but it is speculated to be caused by combined effects of susceptibility genes like familial PD genes and unknown exogenous factors such as nutrition and toxic environmental substances. The following mechanisms are considered: mitochondrial dysfunction, endoplasmic reticulum (ER) stress due to production of misfolded proteins, abnormal degradation of toxic oligomers of misfolded proteins caused by dysfunction of intracellular protein degradation systems including the ubiquitin-proteasome system and autophagy-lysosome system, excitotoxicity, and oxidative stress. Mitochondrial dysfunction in sporadic PD is supported by the findings of mitochondrial complex I deficiency in the nigro-striatum of postmortem brains from sporadic PD patients and inhibition of complex I in the SN mitochondria of animal PD models produced by treatment with neurotoxins. Mitochondrial dysfunction causes the production of free radicals, ROS. Abnormal degradation of misfolded proteins due to dysfunction of the caspase-independent autophagy-lysosome system and/or caspase-dependent ubiquitin-proteasome system might cause the formation of toxic oligomers of α -synuclein to Lewy bodies and dopaminergic cell death in the SN.

Another remarkable pathological mechanism operating in PD and in most other neurodegenerative diseases is the neuroinflammation that accompanies the activation of microglia, which cells, once activated, release various pro-inflammatory cytokines such as tumor necrosis factor (TNF)- α , interleukin (IL)-1 β , and IL-6 (Nagatsu and Sawada M., 2005). The significance of neuroinflammation in AD and PD was proposed for the first time by

McGeer et al. in 1988. The present review will discuss the pathological significance of neuroinflammation in neurodegenerative diseases, especially in PD.

2. Neuroinflammation in Parkinson's disease

One of the neurodegenerative mechanisms at work in PD is the neuroinflammatory process. McGeer et al. (1988) were the first to report that the number of major histocompatibility complex (MHC) class II of human leukocyte antigen (HLA-DR)-positive activated microglia are observed in the SN along with the appearance of Lewy bodies and free melanin in sporadic PD brains. Various dopaminergic neurotoxins including MPTP, 6-OHDA, paraquat, and rotenone used to produce animal models of PD also cause the neuroinflammation that accompanies microglial activation.

Changes in the levels of cytokines, apoptosis-related proteins, and neurotrophins, detected by use of the enzyme-linked immunosorbent assay (ELISA), were reported to have occurred in the postmortem brain (striatum or SN) and/or cerebrospinal fluid (CSF) in sporadic PD patients (Mogi et al., 1994a, 1994b, 1996, 2000; Nagatsu, 2002; Nagatsu and Sawada M., 2005, 2006; Sawada M. et al., 2006); increased levels of cytokines and apoptosis-related proteins, such as TNF- α , IL-1 β , IL-2, IL-4, IL-6, epidermal growth factor (EGF), transforming growth factor (TGF)- α , TGF- β , soluble FAS, TNF- α receptor 1 (p55), Bcl-2, caspase 1, and caspase 3; decreased levels of neurotrophins nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF). An increased level of IL-1 β and decreased level of NGF in the striatum were also reported in MPTP-administered mice (Mogi et al., 1998).

Imamura et al. (2003) reported, based on their immunohistochemical study on PD brains, that MHC class II-positive activated microglia produced TNF- α and IL-6 in the putamen and SN, where damaged TH-positive dopaminergic neurons and neurites were associated with the pathology. In normal brain, there were few MHC class II-positive microglia in the putamen and SN. MHC class II-positive microglia became increased in number with the progression of neurodegeneration in these regions of PD patients. However, such microglia were also associated with non-degenerated dopaminergic neurites, and serotonergic or other neurites without neurodegeneration in PD brains. Moreover, significantly higher number of MHC class II-positive microglia were also observed in the hippocampus and cerebral cortex, where no cell death occurs in the examined PD brains. These immunohistochemical results suggest that activated microglia in the hippocampus and cerebral cortex in PD may be non-toxic or even neuroprotective in contrast to their neurotoxic role in the putamen and SN.

Imamura et al. (2005) further observed activated microglia both in the movement-regulating nigro-striatum and memory-regulating hippocampus in the brains from patients with DLB. In these patients, the levels of BDNF mRNA and immunochemically detected BDNF protein were significantly decreased in the hippocampus, where cell death occurs in DLB; but they were not decreased in the PD hippocampus. The mRNA level of IL-6 was greatly increased in the hippocampus of both PD and DLB patients compared with that for the normal controls. These results suggest that activated microglia in the hippocampus in PD might be non-toxic, or even neuroprotective in contrast to their neurotoxic effect in DLB.

Some systemic viral infections may also cause PD with neuroinflammation. Recently, C57BL/6J mice infected with H5N1 influenza virus were found to display acute neurological signs of mild encephalitis to coma (Jang et al., 2009). In this study, H5N1 virus had invaded from the peripheral nervous system (PNS) into the central nervous system

(CNS) spreading to higher levels of the neuroaxis. They observed activation of microglia, α -synuclein phosphorylation and aggregation, and dopaminergic neuron loss in the SN after long-term progression of the viral infection.

3. Neuroinflammation and microglia

Microglia are derived from myeloid cells having the property of high affinity for the brain and comprise about 10% of the total cells in CNS parenchyma (Ono et al., 1999; Sawada M. et al., 1998). Microglia play important physiological roles in the development, differentiation, and maintenance of neural cells in the brain. They also have immunological functions in the brain and serve to remove dead cells by phagocytic activity after brain injury or neurodegeneration. Microglia are normally in the resting stage, but are activated by some brain lesions in neurodegenerative diseases such as PD.

Activated microglia may play neurotoxic roles by producing pro-inflammatory cytokines such as TNF- α , IL-1, and IL-6, as well as, nitric oxide (NO) and ROS (Cassarino et al., 1997; Chao et al., 1992; Hunot et al., 1996; Kim et al., 2000; Koutsilieri et al., 2002; Liu et al., 1998; McGuire et al., 2001). On the other hand, activated microglia may also function neuroprotectively by producing neurotrophic components such as IL-10, TGF- β , plasminogen, glial cell line-derived neurotrophic factor (GDNF), BDNF, and NGF (Batchelor et al., 1999; Elkabes et al., 1996; Miwa et al., 1997; Nagata et al., 1993b; Nakajima et al., 2001; Sawada M. et al., 1995, 1999; Suzumura et al., 1993).

Pro-inflammatory cytokines such as TNF- α , IL-1 β , and IL-6 are pleiotropic, and may produce either neurotoxic or neuroprotective effects (Arai et al., 2004; Barger et al., 1995; Bolin et al., 2002; Fisher et al., 2001; Liu et al., 1998; Mason et al., 2001; McGuire et al., 2001). TNF- α produced by microglia or astrocytes in the CNS is generally considered to be neurotoxic (Sawada M. et al., 1989; Suzumura et al., 1999). Microglial production of TNF- α is increased when the cells are stimulated with lipopolysaccharide (LPS; Sawada M. et al., 1989, 1995). Neurotoxin-mediated damage to dopaminergic neurons is attenuated in mice deficient in TNF- α or TNF receptors compared with the damage seen in wild-type mice (Ferber et al., 2004; Sriram et al., 2002). A recent study demonstrated that inhibition of TNF reduce the delayed and progressive neurodegeneration in the SN in PD rats (Harms et al., 2011). Two weeks after having received intrastriatal administration of 6-OHDA, PD model rats were injected in their SN with lentivirus encoding a dominant-negative TNF gene. The effects of this abnormal TNF included inhibition of the progressive loss of nigral dopaminergic neurons, when the rats were examined 5 weeks after the initial 6-OHDA administration. The lentivirus dominant-negative TNF therapy also attenuated microglial activation in PD rats. However, some other reports suggest opposite neuroprotective effects of TNF- α . For example, auto-immune-mediated demyelination model mice of multiple sclerosis with deficient TNF- α developed more severe neurological impairment than the normal multiple sclerosis model mice (Liu et al., 1998). Two different subtypes of the TNF receptors may act for neuronal death or survival by different signal transduction pathways (Yang et al., 2002).

LPS is a gram-negative bacterial endotoxin and is a microglial activator substance. LPS treatment causes neurotoxic effects on dopaminergic neurons in various cell culture systems (Gao et al., 2003; Gayle et al., 2002; Kim et al., 2000) or by direct injection into the SN (Arai et al., 2004; Castano et al., 2002; Iravani et al., 2005). LPS is recognized as an

initiator of dopaminergic neuronal loss, and the degree of neuronal damage may depend on the concentration of LPS used for treatment. The neurotoxicity of microglia is increased by the production of $\text{TNF-}\alpha$ in response to LPS stimulation (Sawada M. et al., 1989, 1995). On the other hand, the neurotrophic effects of microglial activation induced by LPS have also been found in several cell culture studies (Elkabes et al., 1998; Kramer et al., 2002; Mallat et al., 1989; Miwa et al., 1997; Nakajima et al., 2001). The neurotrophic effects of LPS may be explained by the fact that LPS induces the secretion of not only pro-inflammatory cytokines but also neurotrophic compounds. Stimulation by LPS increases the microglial secretion of NT-3, NT-4/5, NGF, and BDNF (Elkabes et al., 1998; Miwa et al., 1997; Nakajima et al., 2001). A rat model of spinal cord injury showed improvement in locomotor function by an LPS-elicited increase in the level of neuroprotective GDNF (Hashimoto et al., 2005). Plasminogen produced by LPS-treated microglia was reported to promote the development of dopaminergic neurons (Nagata et al., 1993b; Nakajima et al., 1992).

Several studies indicate that damaged dopaminergic neurons release various factors that can activate microglia. These factors are α -synuclein, matrix metalloproteinase 3 (MMP-3), and neuromelanin, all of which are released from damaged dopaminergic neurons and induce ROS production. α -Synuclein, which is a synaptic vesicle protein and a main component of Lewy bodies, the pathological hallmark of PD, may have an important role in both the onset and progression of PD. Extracellular aggregated α -synuclein induced microglial activation that enhanced neurotoxicity toward dopaminergic neurons, whereas low concentrations of α -synuclein failed to be neurotoxic (Zhang et al., 2005). Microglial enhancement of α -synuclein-mediated neurotoxicity depended on the phagocytosis of α -synuclein and production of ROS by microglia. Nitrated/oxidized α -synuclein was detected in nigral cytoplasmic inclusions, and inhibition of microglial-derived NO and superoxide provided significant neuroprotection to dopaminergic neurons (Gao et al., 2008). MMP3 is a zinc-dependent proteolytic enzyme that degrades the extracellular matrix; and it is released from damaged neurons, thereby inducing microglial activation with production of inflammatory cytokines such as $\text{TNF-}\alpha$ (Kim et al., 2005). MMP-3-deficient mice show reduced MMP-3-induced microglial production of NADPH oxidase-derived superoxide and dopaminergic cell death (Kim et al., 2007).

Microglial activation accompanied by the degeneration of dopaminergic neurons is an early event of neuroinflammation in PD. Purisai et al. (2007) reported that activation of microglia accompanied by the induction of NADPH oxidase was a priming event in paraquat-administered mice, which activation occurred at least 1 or 3 days after the administration. An *in vivo* positron emission tomography (PET) study imaging, microglial activation in nigro-striatal regions indicated that the activation was likely to occur early in the disease process and paralleled the loss of terminals in dopaminergic neurons, as revealed by use of $[^{11}\text{C}](\text{R})\text{-PK11195}$, a peripheral benzodiazepine receptor-binding ligand (Gerhard et al., 2006). However, microglial activation by chronic LPS infusion into the SN or single systemic injection in animals caused delayed and progressive neurodegeneration of nigral dopaminergic neurons (Gao et al., 2002; Qin et al., 2007). Using conditional amyotrophic lateral sclerosis (ALS) transgenic mice, Boillée et al. (2006) demonstrated that microglia had a great effect on the later phase of disease progression but little effect on the early phase of the disease.

4. Neuroprotective role of microgliae

Neurotrophic effects of microglial activation were reported in cell-culture studies (Elkabes et al., 1996, 1998; Miwa et al., 1997; Nagata et al., 1993a; Nakajima et al., 2001) and in studies using animal models of neurodegeneration (Hashimoto et al., 2005; Imai et al., 1999, 2007; Rabchevsky and Streit, 1997; Suzuki et al., 2001).

Fig. 1. Morphological changes due to MPTP administration in the SN. Immunostaining for tyrosine hydroxylase (TH)-positive dopaminergic (A9) neurons (green) and CD 11b-positive activated microglia (red) in the SN from mice treated with saline, MPTP, and LPS-MPTP are shown. In neonatal (P8) mice (A-C), dopaminergic (A9) neurons in the SN were decreased in MPTP-treated mice, whereas these neurons in the LPS-MPTP-treated mice were recovered, compared from MPTP-treated mice. The activated microglia had increased in number in the entire SN in mice treated with LPS-MPTP, as compared with saline- or MPTP-treated mice. In aged (60w) mice (D-F), numbers of the dopaminergic (A9) neurons were decreased in the order of saline, MPTP, and LPS-MPTP treatments. In the MPTP- and LPS-MPTP-treated mice, numbers of the activated microglia were increased with their accumulation in the SNc. P8 refers to postnatal day 8; and 60w, to 60-day-old mice (Sawada H. et al., 2007, *J Neurosci Res*, Vol. 85, No. 8, pp. 1752-1761, With permission of John Wiley and Sons).

Neonatal microglia are activated macrophage colony-stimulating factor (M-CSF)-dependently from late gestation up to two weeks after birth, and are very proliferative and easily activated under normal circumstances (Sawada M. et al., 1990; Thery et al., 1990). Sawada H. et al. (2007) showed that in MPTP-administered neonatal mice their microglia activated by treatment with systemic LPS showed neurotrophic potential toward dopaminergic neurons. Neonatal (postnatal day 7) mice treated with MPTP showed decreases in the number of dopaminergic (A9) neurons in the SN (Fig. 1 and 2), TH activity, and the levels of DA and the metabolite 3,4-dihydroxyphenylacetic acid in the midbrain. However, cell viability of dopaminergic (A9) neurons and these markers increased in mice treated with MPTP and LPS, along with marked LPS-induced activation of microglia (Fig. 1 and 2). A modest activation of microglia and a significant decrease in the number of

dopaminergic (A9) neurons were observed in the MPTP-treated mice, whereas mice treated with the MPTP and LPS demonstrated marked microglial activation and a tendency toward recovery against cell toxicity, as compared with the MPTP-treated mice (Fig. 3A). These MPTP-LPS-treated mice showed increased levels of pro-inflammatory cytokines of IL-1 β and IL-6. LPS-activated microglia in neonatal and aged mice had different phenotypic effects on dopaminergic neurons exposed to MPTP. In contrast, the number of dopaminergic neurons in the SN in aged mice (60 weeks) treated with MPTP was significantly decreased, and an increase in the number of microglia treated with MPTP and LPS produced a further decrease in the number of dopaminergic neurons (Fig. 1 and 2). The relationship between microglial activation and viability of dopaminergic (A9) neurons for the three groups (saline control, MPTP treated, and MPTP-LPS treated mice) of aged mice showed an inverse correlation (Fig. 3B). These results suggest that LPS-activated microglia in aged mice may be neurotoxic, whereas in neonatal mice they may have neurotrophic potential.

Fig. 2. Analysis of effects of LPS treatment on numbers of dopaminergic (A9) neurons and CD 11b-positive activated microglia in MPTP-treated neonatal and aged mice. **A:** Number of dopaminergic (A9) neurons of the SN for the saline, MPTP, and LPS-MPTP groups in P8 mice. The number of dopaminergic (A9) neurons in the MPTP group was significantly decreased, whereas that for the LPS-MPTP group was recovered. **B:** Number of CD11b-immunopositive microglial cells in the SN in P8 mice. The LPS-MPTP group demonstrated marked microglial activation. **C:** Number of dopaminergic (A9) neurons of the three groups in the SN of 60w mice. The number in the MPTP and LPS-MPTP groups was significantly decreased. **D:** Number of CD11b-immunopositive microglia for the three groups in the SN of 60w mice. Severe microglial activation was observed in the LPS-MPTP group. Values represent the mean $\pm$ SD. * p < 0.05; ** p < 0.01 versus saline group, ## p < 0.01 versus MPTP group, by the use of the unpaired Student's t test (Sawada H. et al., 2007, J Neurosci Res, Vol. 85, No. 8, pp. 1752-1761, With permission of John Wiley and Sons).

Using an ischemic gerbil model, Imai et al. (2007) also showed neuroprotective effects of exogenously administered microglia. Microglia cells were isolated from neonatal gerbils by labeling with a fluorescent dye. When the isolated microglia were systemically injected into the subclavian artery in experimental ischemic gerbils, the cells migrated to ischemic hippocampal regions (CA1 pyramidal neurons); and the number of surviving hippocampal neurons was greater in the host gerbils than in the control ischemic animals. This neuroprotective effect was enhanced when the isolated microglia were stimulated by interferon- γ . Administration of exogenous microglia to the ischemic gerbils improved the performance of the animals in a passive-avoidance learning task. The ischemic animals revealed increased expression of neurotrophic factors BDNF and GDNF in their hippocampal regions. Thus, administration of isolated neonatal microglia may potentially have neurotrophic effects on injured brain regions.

Recently, Saijo et al. (2009) reported that an orphan nuclear receptor, Nurr1, protected dopaminergic neurons against impairment by inhibiting the expression of pro-inflammatory mediators produced by microglia and astrocytes, such as TNF- α , IL-1 β , and inducible NO-synthesizing (iNOS) enzyme. Nurr1 is known to play an essential role in the generation and maintenance of dopaminergic neurons. When Nurr1 expression was reduced by shRNA, inflammatory substances were increased in microglia; and with further amplification by astrocytes, these substances caused dopaminergic neuron death in the SN.

Fig. 3. Relationship between activated microglia and dopaminergic (A9) neurons in saline, MPTP, and LPS-MPTP groups of individual neonatal or aged mice. **A:** In P8 mice, only slight activation of microglia and decrease in number of dopaminergic (A9) neurons were found for the MPTP group, whereas the LPS-MPTP group demonstrated marked microglial activation and a tendency toward protection against loss of dopaminergic (A9) neurons compared with the MPTP group. **B:** In 60w mice, an inverse correlation ($R=0.81$) was observed between the 2 parameters when data for all 3 groups was plotted (Sawada H. et al., 2007, J Neurosci Res, Vol. 85, No. 8, pp. 1752-1761, With permission of John Wiley and Sons).

The question as to whether or not peripheral macrophages or lymphocytes can cross the BBB into the PD brain remains still controversial. However, peripheral T lymphocytes have

been reported to be relevant to the pathogenesis of PD in relation to microglia. The infiltration of peripheral immune cells into the brain and its relevance to PD have been reported. Infiltrates of CD4⁺ T cells were found in the SN of PD patients, and CD4⁺ T cells were neurotoxic in MPTP-treated mice (Brochard et al., 2009). In contrast, mice lacking CD4⁺ T cells showed attenuated nigro-striatal degeneration induced by MPTP. Another report indicated that nitrated α -synuclein, which is abundant in Lewy bodies, was detected in peripheral lymphocytes in cervical lymph nodes from MPTP-treated mice (Benner et al., 2008). The transfer of T cells from mice immunized with nitrated α -synuclein into MPTP-treated mice caused significant infiltration into the brain and a neuroinflammatory response with accelerated dopaminergic neuron loss (Benner et al., 2008). The consequence of two subsets of CD4⁺ lymphocytes that acted on microglia was reported to be different (Reynolds et al., 2009). In the presence of nitrated α -synuclein, one subset, i.e., CD4⁺ CD25⁻ (effector) T cells, enhanced the microglial activation and neurotoxic responses by secreting TNF- α and IFN- γ ; and the other, CD4⁺ CD25⁺ (regulatory) T cells, suppressed the microglia activation and induced microglia apoptosis by secreting IL-10 and TGF- β . On the other hand, the Th1 and Th17 cells, other subsets of CD4⁺ T cells, increased the production of NO, superoxide, TNF- α and IL-1 β from microglia, and decreased the production of neurotrophic factors such as insulin-like growth factor (IGF)-1 (Appel, 2009). Consequently, neuronal injury, which may trigger the release of increased levels of nitrated α -synuclein, may enhance the microglia-mediated neurotoxicity. CD4⁺ CD25⁺ T cells suppressed the inflammatory effects of Th17 cells. Another subset of CD4⁺ T cells, Th2 cells, produced IL-4, increased the release of IGF-1 from microglia, and decreased the release of free radicals, resulting in enhanced neuronal protection.

5. Neurotoxic role of microglia

Many reports on postmortem PD brains and PD animal models indicate that activated microglia have neurotoxic effects and may play a significant role in progression of the disease (Block et al., 2007). Microglial activation was also reported to be neurotoxic in experimental PD models produced by MPTP (Furuya et al., 2004; Wu et al., 2002, 2003).

ROS production from microglia adversely affects the neurons. Previous studies demonstrated that NADPH oxidase-mediated microglial superoxide production is important to MPTP- or rotenone-induced dopaminergic toxicity (Gao et al., 2003; Wu et al., 2002, 2003). NADPH oxidase subunit (gp91)-deficient mice showed attenuated microglial production of superoxide and dopaminergic cell death (Wu et al., 2003).

There have been many reports indicating the neurotoxic effects of activated microglia, especially in aged animals (Sawada H. et al., 2007; Sawada M. et al., 2008; Sugama et al., 2003). Aging is thought to be an important factor in idiopathic PD. Aging is speculated to promote a change from the protective to the toxic phenotype of activated microglia, as in the toxic change in microglia hypothesized by Sawada M. et al. (2006). Cultures of amyloid β -peptide (A β)-stimulated microglia from aged rats were reported to show more evidence of toxicity than those from middle-aged or embryonic mice (Viel et al., 2001). Furthermore, MPTP neurotoxicity is greater in aged mice than in young mice, and is accompanied by age-related microglial activation (Sugama et al., 2003).

As described above, activated microglia acted in neuroprotection in MPTP-treated neonatal mice. However, microglia in neonatal or young animals might also act as neurotoxicity, depending on the condition of microglial activation. Sawada H. et al. (2010) reported that

LPS-activated neonatal microglia showed the neurotoxic phenotype in an ethanol-induced brain injury model produced by the stereotaxic injection of ethanol into the mouse striatum (Takeuchi et al., 1998; Toyama et al., 2008; Fig. 4). In this ethanol-injected model produced a large and round or oval shaped brain lesion without hemorrhage, infection or other unexpected effects that might affect the cytokine networks in the brain. Neonatal mice were pretreated with systemic LPS or saline injection (i.p.) daily for 5 days from postnatal day 3 (P3) to P7. Local injection of 100% ethanol (2.0 μ l) produced more severe neuronal damage than seen in the MPTP-induced PD model. A large lesion with a necrotic core was observed in the ethanol-injected striatum; and activated microglia had migrated to the outside of this necrotic mass, where Fluoro-Jade B (FJB)-positive degenerative neurons were observed (Fig. 4). After the ethanol-induced damage, activated microglia accumulated in the FJB-positive regions and eliminated damaged neurons by causing delayed neuronal death (Fig. 4). By previous treatment with systemic LPS or saline treatment as a control, the volumes of necrotic and degenerative areas in the striatum were further increased along with an increase in the number of activated microglia by LPS (Table 1). The number of iNOS-positive microglia also tended to be increased by the LPS treatment.

Fig. 4. Morphological changes due to ethanol injection into the striatum of neonatal (P8) mice; detection of neuronal injury by Fluoro-Jade B (FJB) staining and activated microglia by CD11b immunostaining. A large diameter of lesion was observed in ethanol-injected striatum 24 hr after the injection with the core of necrotic mass. Degenerative cells were observed outside the necrotic mass. **A:** In FJB staining, many FJB-positive cells were seen in the degenerative region. **B:** In CD11b immunostaining, the large number of activated microglia was found in the degenerative region. n; necrotic region, d; degenerative region. FJB-positive degenerative neurons are shown in saline-treated (C), and LPS-treated (D) mice. The number of FJB-positive degenerative cells was increased in LPS-treated mice. CD11b-positive microglia in ethanol-injected ipsilateral striatum are shown in saline-treated (E), and LPS-treated (F) mice. Increase in the number of activated microglia was observed most markedly in LPS-treated mice.

	Necrotic volumes (mm ³)	FJB (+) volumes (mm ³)	CD11b (+) cells (number/ mm ²)
Saline-treated	0.297±0.137	0.529±0.336	104.5±17.7
LPS-treated	0.696±0.281 *	1.443±1.136	210.6±51.7 **

Table 1. Volumes of the necrotic or FJB positive areas and number of the CD11b positive microglia in ethanol-injured striatum. These data are obtained from 4-5 of neonatal P8 mice. Values represent the mean±SD. * *p* < 0.05; ** *p* < 0.01, by use of the unpaired Student's *t* test.

6. Toxic change in microglia

Sawada M. et al. (1998, 1999, 2006) proposed a hypothesis of toxic change of microglia. He with collaborators separated two subsets of microglia with neuroprotective or neurotoxic phenotypes from mouse brain by cell sorting and established a cell line for each. The 6-3 cell line of one subset produced a greater amount of ROS stimulated by phorbol myristate acetate (PMA) than did the other, the Ra2 cell line. Both clones were dependent on granulocyte macrophage colony-stimulating factor (GM-CSF). When both microglia cell lines were co-cultured with N18 neuronal cells, which are sensitive to oxidative stress by hydrogen peroxide to produce dose-dependent cell death, and are stimulated with PMA, the viability of the N18 cells was increased when the cell were co-cultured with Ra2 cells and decreased in the presence of 6-3 cells. These results indicate that 6-3 cells were of the neurotoxic phenotype, and that Ra2 cells were of neuroprotective one.

A toxic change in microglia phenotypes from neuroprotection to neurotoxicity was observed by transfecting the cells with cDNA encoding HIV-1 Nef protein, indicating the conversion of microglia from a neurotrophic to a neurotoxic subtype (Vilhardt et al., 2002). When Ra2 cells were transfected with Nef protein by using lenti virus, these normally neuroprotective cells produced ROS with activation of NADPH oxidase, in contrast to the non-transfected Ra2 cells, which did not produce ROS. When Nef-Ra2 cells were co-cultured with N-18 neuronal cells, the viability of N-18 cells was decreased; whereas that of N-18 cells co-cultured with Ra2 cells was not lowered. These results suggest a toxic change in nef-transfected microglia accompanied by ROS production.

According to a report on conditional ALS transgenic mice, the disease progression was determined by the expression of mutant superoxide dismutase (SOD)1 protein not in motor neurons but in microglia (Boillée et al., 2006). Microglial activation was observed from the disease onset to the progression in the spinal cord in these animals. The disease progression accelerated in the transgenic mice that expressed mutant SOD1 in all systemic cells including microglia, whereas the viability was improved in the transgenic mice that expressed normal SOD1 only in their microglia. However, the early phase of disease progression showed no difference between above the two types of transgenic mice. This report concluded that microglia had little effect on the early disease phase but participated on the later disease progression in ALS. According to the hypothesis of toxic change in microglia by Sawada M., microglial toxic changes might appear during the progression phase of ALS.

Lai and Todd (2008) examined the effect of microglia by changing the severity of hypoxia-induced neuronal injury in a culture study. After exposing neuronal cells to various degrees of hypoxia, i.e., mild, moderate, or severe, the media from the neuronal cell culture were added to microglial cell culture. Neuroprotective phenotype of microglia was observed with the media from neurons with moderate hypoxia, but not with those from the cultured cells under mild or severe hypoxia.

Fig. 5. This scheme shows a hypothesis of toxic change of microglia by two step activation of microglia proposed by Sawada M. et al. At the first step, activated microglia by the first stimulation probably by signaling molecules from injured neurons produce such as neurotrophins, neurotrophic cytokines, antioxidant, and may act for neuroprotection. At the secondary step, activated microglia, which are further stimulated by other factors such as a large amount of cytotoxic factors, may produce toxic change of microglia, which converts neuroprotective phenotypes to neurotoxic ones.

Inoue (2002) hypothesized that the fate of damaged neurons may be regulated in part by ATP through the activation of microglia. Microglia possess the functional P2 receptors, P2X and P2Y, which bind to purines and pyrimidines. Microglial activation is triggered by extracellular ATP or ADP, which is released from damaged neurons under pathological situations. Microglia showed membrane ruffling and enhanced chemotaxis in response to extracellular ATP or ADP produced by neuronal injuries (Honda et al., 2001). A low concentration of extracellular ATP (10-100 μ M) stimulated microglial secretion of a neurotrophic substance plasminogen, with a peak response at 5-10 min after the stimulation. This secretion was ATP-concentration dependent (Inoue et al., 1998).

Thereafter, ATP at low-to-moderate concentrations (maximal secretion at 1 mM) stimulated TNF- α secretion from microglia, beginning at 2-3 hr after the stimulation (Hide et al., 2000). About 6 hr after the stimulation with ATP, the microglia showed increased release of IL-6, which secretion was ATP concentration dependent (10-1,000 μ M; Shigemoto-Mogami et al., 2001). ATP also induced an increase in Ca²⁺ influx in a concentration-dependent manner. Furthermore, after the stimulation at high concentrations of ATP (10-1,000 μ M) about 12 hr later microglial iNOS synthesis was induced; and this iNOS produced NO, then killed neuronal cells (Ohtani et al., 2000). Therefore, initial weaker and shorter stimulation of microglia by extracellular ATP may lead to neuroprotection by secretion of plasminogen, TNF- α , and IL-6; whereas stronger and longer exposures to ATP may be neurotoxic due to NO production. A recent report demonstrated that delayed neural damage was induced by iNOS expression by microglia in brain injured mouse model (Ono et al., 2010). Microglia themselves also release ATP depending on the LPS concentration (Ferrari et al., 1997).

As described above, Sawada M. et al. (2006) hypothesized that the microglial activation may occur in two steps in the PD brain (Fig. 5). At the first step, microglia activated by the first stimulation probably by signaling molecules from injured neurons produce neuroprotectants such as neurotrophins, neurotrophic cytokines, and antioxidant. At the secondary step, activated microglia, which are further stimulated by other factors such as a large amount of cytotoxic factors, may undergo toxic changes, thus converting them from the neuroprotective phenotype to the neurotoxic one, with the result being neuronal cell death in PD.

7. Conclusions

Neuroinflammation with activated microglia may play important roles in the pathogenesis of various neurodegenerative diseases including PD. Activation of microglia may be produced by some chemical signaling molecules released from the injured neurons such as dopaminergic neurons in the SN of the PD brain. Activated microglia may be neuroprotective, at least in the early phase, but may become neurotoxic later to contribute to the progression of the disease. Sawada M. et al. proposed a hypothesis of a toxic change in activated microglia from the neuroprotective phenotype to the neurotoxic one. Development of drugs to regulate activated microglia could be a promising approach for drug development for neurodegenerative diseases such as PD.

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This book about Parkinson's disease provides a detailed account of etiology and pathophysiology of Parkinson's disease, a complicated neurological condition. Environmental and genetic factors involved in the causation of Parkinson's disease have been discussed in detail. This book can be used by basic scientists as well as researchers. Neuroscience fellows and life science readers can also obtain sufficient information. Beside genetic factors, other pathophysiological aspects of Parkinson's disease have been discussed in detail. Up to date information about the changes in various neurotransmitters, inflammatory responses, oxidative pathways and biomarkers has been described at length. Each section has been written by one or more faculty members of well known academic institutions. Thus, this book brings forth both clinical and basic science aspects of Parkinson's disease.

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