Neuroprotective and Neurotoxic Roles of Activated Microglia

Activated microglia in the PD brain produce proinflammatory cytokines such as TNF-α and IL-6. Since cytokines have either neuroprotective or neurotoxic effects, a main question is whether activated microglia are neuroprotective or neurotoxic.

Imamura et al. [4] proved, by double immunofluorostaining, the coexistence of cytokines, TNF-α and IL-6, with MHC class II (CR3/43) in ICAM-1- and LFA-1-positive activated microglia in the putamen in PD. Activated microglia were not only observed in the nigrostriatal region with neurodegeneration, but also in other brain regions, such as the hippocampus and cerebral cortex, without significant neurodegeneration. These immunohistochemical observations in PD brains suggest that activated microglia may have either neuroprotective or neurotoxic functions depending upon the brain regions and the stage of disease. Imamura et al. [5] compared the expression of cytokines and neurotrophins in the hippocampus and putamen of postmortem brains from patients with PD or dementia with Lewy bodies (DLB), and normal controls, and suggested that activated microglia in the hippocampus of PD and DLB patients may be different in properties in secreting different kinds and different amounts of cytokines and neurotrophins, such as IL-6 and brain-derived neurotrophic factor, and may be neuroprotective in PD and neurotoxic in DLB.

Neuroprotective and Neurotoxic Functions of Activated Microglia in the Substantia Nigra of Neonatal and Aged Mice, and the PD-Producing DA Neurotoxin 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine

The above data on postmortem brains from PD or DLB patients suggest that activated microglia may have either neuroprotective or neurotoxic functions. It is well known that aging is an important risk factor in PD or DLB.

Sawada et al. [6] have examined the difference between neonatal and aged mice in the in vivo effects of microglia activated by systemic administration of lipopolysaccharide (LPS) on nigrostriatal DA neurons treated with the PD-producing neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). In neonatal mice, microglia activated by treatment with LPS showed a neurotrophic potential toward DA neurons. TH activity and the levels of DA and the metabolite 3,4-dihydroxyphenylacetic acid as well as those of the proinflammatory cytokines IL-1β and IL-6 were elevated in the midbrain of LPS-MPTP-treated neonatal mice. The number of DA neurons in neonatal mice was decreased in the MPTP group, but was recovered in the LPS-MPTP group. In contrast, the number of DA neurons in the aged (60-week-old) mice was decreased by a single MPTP administration in the MPTP group, and was further decreased in the LPS-MPTP group, as compared to the saline group. The MPTP group of aged mice showed a slightly increased number of activated microglia in the substantia nigra; in the LPS-MPTP group, the increase was significant. These results indicate that the cell viability of DA neurons was recovered in neonatal mice of the LPS-MPTP group compared with that of the MPTP group. In contrast, the viability of these neurons in the aged mice dropped significantly comparing the LPS-MPTP group with the MPTP group. Activated microglia in the brain may be neuroprotective in neonatal mice, whereas those in the same group of aged mice may be neurotoxic. LPS treatment performed by systemic injection in these experiments may result in involvement of not only microglia, but also many cells, such as astrocytes, vascular endothelial cells, and in particular T cells. However, since microglia are most rapidly activated by LPS, these results suggest that most probably activated microglia in neonatal mice may have a neuroprotective role, in contrast to the neurotoxic effect of activated microglia in aged mice, and that the activated microglia are different in their properties between neonatal and aged brains. The causative factors are still unknown; it is possible that changes of the neurodegenerating potential and microenvironment including components of extracellular matrices and accumulation of oxidized proteins or lipids may affect the activation process and the state of activated microglia.

Conclusion

Studies on the brain of MPTP-treated mice suggest the existence of toxic and neuroprotective subsets of activated microglia. Activated microglia may be neuroprotective in neonatal mice, but neurotoxic in aged mice. Sawada et al. [3] proposed that the function of activated microglia may change in vivo from neuroprotective to neurotoxic as degeneration of DA neurons in the substantia nigra progresses in PD. This hypothesis on the toxic change of activated microglia had its origin in the in vitro experiments by Vilhardt et al. [7] in collaboration with

Sawada M., which proved that a neuroprotective microglial clone in a culture experiment converted to a toxic microglial clone by transduction of the HIV-1 Nef protein that is related to the pathogenesis of AIDS encephalitis with increasing NADPH oxidase activity. The results in the present review suggest that aging may promote a rapid toxic change in activated microglia by changing the bias of activated microglia.

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