Gene-Environment Interactions in the Etiopathogenesis of Parkinson’s Disease: Role of Inflammation

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Research Abstract

Parkinson’s disease (PD) is a relentlessly progressive disease characterized clinically by bradykinesia, rigidity, and resting tremor. Clinical manifestations of PD are not apparent until 80~85% of neurons in the substantia nigra pars compacta (SNc) have degenerated and striatal dopamine (DA) levels are depleted by 60~80%. At the time of diagnosis, the therapeutic window and the potential to intervene are therefore greatly reduced. Thus, there is an urgent need to understand better the pathogenetic basis of PD so that effective early neuroprotective therapies can be developed. There are many diverse genetic and age-associated risk factors for developing PD. Converging evidence, including the reduced risk for PD among long-term users of nonsteroidal anti-inflammatory drugs, strongly supports the role of inflammation in PD pathogenesis.

The current research proposal aims to define the role of inflammation in the etiopathogenesis of sporadic and familial PD. By the means of a series of novel transgenic mice, we will dissect the role of different immune cells subsets in the initiation of neuron dysfunction and degeneration.

To investigate whether genetic vulnerability combined with inflammation could underlie the patterns of neuron degeneration seen in PD, we will focus on the commonest form of hereditary PD which relates to mutations in the Leucine-rich repeat kinase 2 (LRRK2) gene. Induced pluripotent stem cells (iPSC) generated from skin cells of LRRK2-PD patients, and novel transgenic mice overexpressing human LRRK2 in specific neuronal and immune cell populations, will allow us to investigate the non-cell autonomous mechanisms involved in the disease onset.

Such in vivo and in vitro models of sporadic and hereditary PD provide promising experimental situations in which to investigate the subtle changes of the preclinical stages of the disease, as well as the identification of early disease biomarkers and potential new therapeutic agents.

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