

An anti-Oxidative Stress Protein DJ-1 and Parkinson's Disease

○Hiroyoshi Ariga¹, Takahiro Taira^{1,4}, Yoshihisa Kitamura² and Sanae M.M. Iguchi-Ariga³

(¹Grad. Pharm., Hokkaido Univ., ²Dept. Neurobiol., Kyoto Pharm. Univ., ³Grad. Agr., Hokkaido Univ. and ⁴Grad. Med. Yamanashi Univ.)

DJ-1 has recently been shown to be responsible for onset of familial Parkinson's disease (PD), PARK7. We have shown that DJ-1 plays roles in transcriptional regulation and anti-oxidative stress, and loss of its function is thought to trigger onset of PD. We and others have also shown that some DJ-1 is located in mitochondria in addition to the cytoplasm and nucleus and that translocation of DJ-1 to mitochondria was stimulated by oxidative stress. Furthermore, we found that DJ-1 was a positive regulator of the mitochondrial complex 1 by binding to its subunit.

When a recombinant DJ-1 protein was administrated into the brain of PD model rats that had been injected to 6-hydroxydopamine (6-OHDA) in the left substantia nigra, PD phenotypes, including dopaminergic neuron death both in the substantia nigra and striatum, decrease in dopamine and dopamine transporter levels in the striatum, and motor abnormality, were dramatically improved by wild-type DJ-1 but not L166P DJ-1, a mutant form of DJ-1 found in PD patients. Furthermore, production of reactive oxygen species and cell death induced by 6-OHDA in SH-SY5Y cells were inhibited by addition of the recombinant DJ-1. We then screened low-molecular weight compounds that bind to the catalytic region of DJ-1 and found that these compounds protected SH-SY5Y cells from oxidative stress-induced cell death by inhibiting oxidation of DJ-1. These findings suggest that DJ-1 and its binding compounds are therapeutic targets for PD.