# PARK7

DJ-1 (also called PARK7) is an oxidation sensitive protein encoded by the PARK7 gene. Mutations in PARK7 are a rare cause of familial recessive Parkinson's disease (PD), but growing evidence suggests involvement of DJ-1 in idiopathic PD. The key clinical features of PD, rigidity and bradykinesia, result from neurotransmitter imbalance, particularly the catecholamines dopamine (DA) and noradrenaline. We report in human brain and human SH-SY5Y neuroblastoma cell lines that DJ-1 predominantly forms high molecular weight (HMW) complexes that included RNA metabolism proteins hnRNPA1 and PABP1 and the glycolysis enzyme GAPDH. In cell culture models the oxidation status of DJ-1 determined the specific complex composition. RNA sequencing indicated that oxidative changes to DJ-1 were concomitant with changes in mRNA transcripts mainly involved in catecholamine metabolism. Importantly, loss of DJ-1 function upon knock down (KD) or expression of the PD associated form L166P resulted in the absence of HMW DJ-1 complexes. In the KD model, the absence of DJ-1 complexes was accompanied by impairment in catecholamine homeostasis, with significant increases in intracellular DA and noraderenaline levels. These changes in catecholamines could be rescued by re-expression of DJ-1. This catecholamine imbalance may contribute to the particular vulnerability of dopaminergic and noradrenergic neurons to neurodegeneration in PARK7-related PD. Notably, oxidised DJ-1 was significantly decreased in idiopathic PD brain, suggesting altered complex function may also play a role in the more common sporadic form of the disease [1)].

TAR DNA-binding protein 43 (TDP-43) is a major protein component of pathological inclusions in amyotrophic lateral sclerosis and frontotemporal dementia. Reducing aberrant aggregation of TDP-43 is a potential approach to prevent cell death. To investigate whether DJ-1 might inhibit TDP-43 aggregation to exert a protective effect in oxidative stress-induced injury, Lei et al. tested the protein level and subcellular localization of TDP-43 and DJ-1 in SH-SY5Y cells transfected with wild-type DJ-1, DJ-1 mutant (L166P) cDNA, or DJ-1 siRNA. They showed that oxidative stress induced by paraquat leads to the formation of cytosolic TDP-43 aggregation in SH-SY5Y cells. DJ-1 overexpression decreases paraquat-induced cytoplasmic accumulation of TDP-43 in SH-SY5Y cells and protects against paraquat-induced cell death. Transfection of DJ-1 L166P mutant or DJ-1 siRNA leads to increased cytosolic aggregation of TDP-43 in paraquat-treated SH-SY5Y cells and promotes cell death. These data suggest that DJ-1 may protect against oxidative stress-induced cell death through the suppression of cytoplasmic TDP-43 aggregation [2)].

1)
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2)
Lei Y, Zhang ZF, Lei RX, Wang S, Zhuang Y, Liu AC, Wu Y, Chen J, Tang JC, Pan MX, Liu R, Liao WJ, Feng YG, Wan Q, Zheng M. DJ-1 Suppresses Cytoplasmic TDP-43 Aggregation in Oxidative Stress-Induced Cell Injury. J Alzheimers Dis. 2018 Oct 22. doi: 10.3233/JAD-180460. [Epub ahead of print] PubMed PMID: 30372676.