Upregulated Parkin expression protects mitochondrial homeostasis in DJ-1 konckdown cells and cells overexpressing the DJ-1 L166P mutation

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Abstract Rare genetic mutations in the DJ-1 and Parkin genes cause recessive Parkinsonism, however, the relationship between these two genes is not fully elucidated. Current emerging evidence suggests that these genes are involved in mitochondrial homeostasis, and that a deficiency in either of these two genes is associated with damages in mitochondrial function and morphology. In this study, we demonstrated that knockdown of DJ-1 expression or the overexpression of the DJ-1 L166P mutation results in a damaged phenotype in mitochondria and a hypersensitivity to H₂O₂-induced cell apoptosis. These phenotypes result from increased levels of endogenous oxidative stress. However, overexpression of wild-type Parkin rescued the phenotypes observed in the mitochondria of DJ-1 knockdown and DJ-1 L166P mutant cells. We also determined that there were differences between the two cell models. Furthermore, both H₂O₂ treatment and the DJ-1 L166P mutation weakened the interaction between DJ-1 and Parkin. Taken together, these findings suggested that DJ-1 and Parkin were linked through oxidative stress, and that overexpression of Parkin protects DJ-1 protein-deficient and DJ-1 L166P mutant-expressing cells via inhibition of oxidative stress.

Keywords Parkinson’s disease · Parkin · DJ-1 · Oxidative dysfunction · Mitochondrial homeostasis

Introduction

Pathogenic mutations in DJ-1, such as the L166P point mutation, contribute to the pathogenesis of autosomal recessive early-onset Parkinsonism [1]. Currently, DJ-1 is a multifunctional protein implicated in several cell processes, including anti-oxidative stress, chaperone activity [2], transcriptional regulation [3, 4], and signal transduction regulation [5, 6]. Despite its many functions, DJ-1 protein has been most extensively studied as an anti-oxidative protein to maintain mitochondrial homeostasis and extensively explored in various models of PD. Wild-type DJ-1 eliminates intracellular reactive oxygen species (ROS) and reduces the level of protein oxidation caused by oxidative stress. Furthermore, knockdown of endogenous DJ-1 renders cells more susceptible to oxidative damages and various insults mediated by toxic agents, such as rotenone, 6-hydroxydopamine, paraquat, and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Further research revealed that in addition to being a ROS scavenger through itself oxidation, DJ-1 also involved in regulating gene expression of some antioxidants [7–9]. These data suggest that DJ-1 is implicated in mitochondrial homeostasis against mitochondrial defects [10], especially considering that excessive ROS damage mitochondrial function and dynamics, and activate mitophagy.

Parkin, another recessive gene of Parkinsonism, encodes an ubiquitin E3 ligase. Recent studies have identified that Parkin and PINK1 function in a common pathway to promote the removal of impaired mitochondria via the autophagy-lysosome pathway [11]. Moreover, Parkin is also involved in mitochondrial biosynthesis [12], mtDNA self-repair [13], and mitochondrial morphology [14, 15]. Parkin exhibits an active role in integrity, function, dynamics, and mitophagy; thus prominently affecting mitochondrial quality control.