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Professor Special Lecture: 154th Regular Meeting of the Medical Society of Toho University

**Review Article**

# Multifunctional Protein DJ-1 and Disease
# - 20 Years since the Isolation of the DJ-1 Gene, and Future Research -

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**ABSTRACT**

We have researched the initiation of DNA replication for many years, and as part of that research, we have performed functional analysis of the oncogene product c-Myc. Therefore, yeast two-hybrid screening was used to search for protein candidates that bind to the c-Myc protein and control its function.

DJ-1 was originally isolated as a c-Myc-binding protein. However, subsequent furthered studies revealed that it did not bind to c-Myc.

At that time, we were routinely performing focus formation analysis. Focus formation analysis was conducted to analyze focus formation efficiency by introducing various genes into mouse NIH3T3 fibroblasts or mouse embryonic fibroblasts in order to examine whether these genes promote carcinogenesis. The DJ-1 gene was used as a negative control. As a result of the experiment, we found that DJ-1 cooperates with *ras* to promote transformation of cells.

In 1997, DJ-1 was reported by us as being a novel oncogene that promotes cell carcinogenesis with ras cooperatively. DJ-1 was named after two students, Daisuke and Junko, who were researching this gene with me.

Furthermore, we have reported the following functions.

1, Significantly increased proteins in testis exposed endocrine disruptors.
2, Positive transcription regulator of androgen receptor.
3, Essential for fertilization.

In 2003, Bonifati et al. reported that DJ-1 (*PARK7*) is a causative gene for familial Parkinson's disease. Thus, it became clear that DJ-1 is a multifunctional protein with various biological functions.

Here, I introduce the findings we have clarified over the past to present of the function of DJ-1 as an oxidative stress defense factor and another functions.

Furthermore, I will introduce the new features of DJ-1 that have been reported in recent years, and introduce possible clinical diagnostic index and the therapeutic drug development based on the DJ-1 protein.

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**KEYWORDS: DJ-1 protein, neurodegenerative disease, Parkinson's disease (PD), oxidative stress**

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## Introduction

In 1997, we reported DJ-1 as a novel gene that promotes cell carcinogenesis in cooperation with *ras*.[1] The amino acid sequence of DJ-1 is highly conserved from Drosophila to human. The human DJ-1 protein consists of 189 amino acid residues and has no specific characteristic amino acid sequence. (Nagakubo D. et al. 1998, unpublished data).

The human DJ-1 gene is located at the 1p36.12-13 locus, and loss of heterozygosity in this region has been reported in many cancers such as gastric cancer, colon cancer, lung cancer, breast cancer, and neuroblastoma.

After we revealed DJ-1 as a novel oncogene and foreign researchers have reported that DJ-1 protein is significantly reduced in the testis of rats, administrated endocrine disruptors.[2, 3].

After this testicular report, we revealed that DJ-1 represses AR negative transcriptional regulator PIAS x alpha and activates AR transcription.[4]

As a result, when DJ-1 in the testis is drastically reduced due to exposure to endocrine disrupters, AR transcription is suppressed, and consequently spermatogenesis inhibition and infertility are induced in mice. Furthermore, the three-dimensional structure of DJ-1 was determined by us and foreign researchers.[5]

In 2003, Bonifati et al., reported that DJ-1 was responsible for familial Parkinson's disease (PD) in an analysis of two Italian families. As a result, DJ-1 was identified as a *PARK7*. The mutation in the DJ-1 reported by Bonifati et al., was a wide deletion in the N-terminal region and a 166th leucine substitution of one amino acid in proline (L166P mutant).

The result of introducing an expression vector in which wild-type DJ-1 gene and L166P mutant were fused to GFP gene into COS7 cells, and examining intracellular localization under a confocal microscope.

The results showed that the wild-type DJ-1 was homogeneously distributed throughout the cytoplasm, whereas the L166P mutant aggregated and accumulated around mitochondria. These aggregates are commonly found in neurodegenerative diseases such as PD and Alzheimer's disease. Mutations in the DJ-1 protein have also been shown to be one of the causes of PD development.[6]

Previously, it was estimated that there were two *PARK6* and *PARK7* and these two genes were close loci on chromosome 1. Groen et al. and Valenta et al. reported that one of the two estimated genes encoded DJ-1 and the other PINK1 (PTEN-induced putative kinase 1).[7, 8]

At present, 18/17 familial PD causative genes have been reported. The onset factor of sporadic PD is known as aging. On the other hand, the onset of familial PD is a mutation in the causative gene.

Analysis of the causes of familial PD and its products can be used to identify not only familial PD but also the causes of sporadic PD and develop treatments.

## Function of DJ-1 Protein in the Onset of PD

DJ-1 expression was high in all human tissues (organs), but was particularly high in the brain, heart, and testis. DJ-1 protein is also abundantly contained in one cell, and it has been revealed that there are 105 to 106 molecules in one cell. (Taira T. et al. 2005, unpublished data).

Subsequently, it has been reported that DJ-1 protein is induced in cultured cells derived from umbilical cord endothelium exposed to the herbicide paraquat that causes oxidative stress.[9, 10]

Furthermore, Wagenfeld et al. reported that DJ-1 is significantly reduced in the testis of rats exposed to several endocrine disrupters. Endocrine disruptors have various effects on living organisms, but it is widely known that endocrine disruptors produce reactive oxygen species (ROS) in cells that have been exposed to them.[11]

In general, degeneration of proteins and mitochondria by ROS is widely known as one of the mechanisms of PD onset. Thus, it was suggested that DJ-1 protein inhibits ROS production in cells and inhibits the cytotoxic function of ROS.

Therefore, human neuroblastoma-derived SH-SY5Y cells were exposed to hydrogen peroxide at a concentration of 0 to 1 mM, and endogenous DJ-1 protein amount and isoelectric point were analyzed by SDS-PAGE and isoelectric focusing (IEF). As a result, it became clear that the DJ-1 protein increased and converted from the reduced form to the oxidized form depending on the concentration of hydrogen peroxide exposed. (Fig. 1).[12]

In general, chemical modification of cysteine in a protein is well known as a mechanism for changing the isoelectric point of a protein. DJ-1 has three cysteine residues at the amino acid positions 46, 53, and 106. Chemical modifications of these three cysteines were analyzed by mass spectrometry.

As shown in Fig. 2, the cysteine residues in the DJ-1

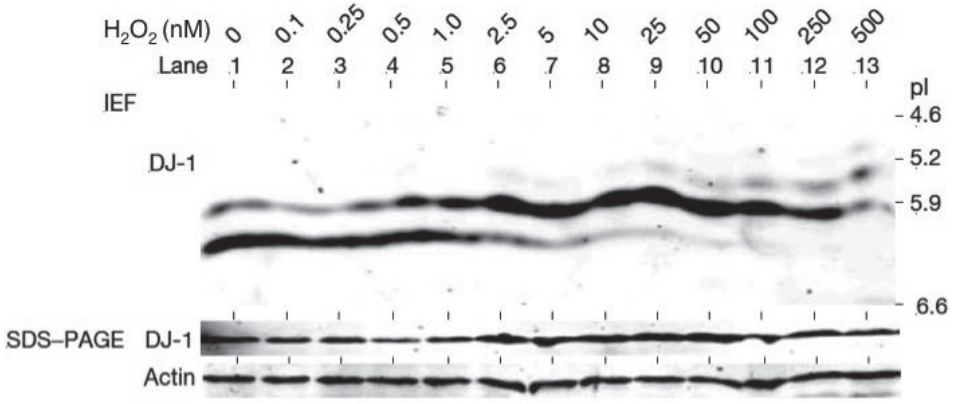


Fig 1. pI shift of DJ-1 after its treatment with hydrogen peroxide. SH-SY5Y cells were treated with various concentrations of hydrogen peroxide for 12 h and proteins in the extracts were then analyzed by isoelectric focusing electrophoresis gel (IEF, upper panel) or PAGE containing SDS (SDS-PAGE, lower panel).


Fig 2. Chemical conversion of cysteine residues in DJ-1 protein.

protein were converted from cysteine to cysteine sulfate and then to cysteine sulfonic acid, depending on the concentration of hydrogen peroxide to be exposed. (Fig. 2). Thus, the ROS scavenging mechanism of the DJ-1 protein absorbs through cysteine modification.[13]

It was revealed that the ROS scavenging mechanism of DJ-1 protein is a completely different mechanism from proteins such as peroxiredoxin, glutathione peroxidase, and catalase that eliminate ROS by known enzymatic reactions.[14]

## Oxidation State of DJ-1 Protein

As in the previous section, DJ-1 protein was found to be in several stages of oxidized form. Unexpectedly, even in the absence of oxidative stress, half of the 106th cysteine of DJ-1 protein was converted to cysteine sulfinic acid (shown in Fig. 2). Zhou et al. reported as follows about this half of the oxidized DJ-1 protein in the without of oxidative stress.[15]

1. Oxidation reaction of the 106th cysteine of DJ-1 to cysteine sulfinic acid is reversible.
2. Only cysteine sulfinic acid type has molecular chaperone function, and the non-oxidative type (reduced type) has no chaperone function.

That is, in the DJ-1 protein, chaperone activity is controlled by conversion between reduced and oxidized forms. Moreover, in addition to the oxidation of the 106th cysteine to sulfinic acid to sulfonic acid in excess, when the 46th and 53rd cysteines, which are not originally site of preferential oxidation, sites, are changed to sulfinic acid, the chaperone function is inactivated and the DJ-1 protein is converted to the insoluble aggregated form. The aggregates accumulated in mitochondria and impaired mitochondrial function. After that, the aggregate was degraded in the cell, but it was revealed that it was degraded in the ubiquitin-proteasome system because it was inhibited by the addition of MG132 (Taira T. et al. 2005, unpublished data).

Dysfunction to mitochondria of over-oxidized DJ-1 protein and L166P mutant protein. Under non-oxidative stress conditions, DJ-1 protein is localized in the cytoplasm. On the other hand, the L166P mutant and extreme oxidized DJ-1 proteins become insoluble and aggregate around mitochondria. Mitochondria are organelles that are constantly exposed to ROS for ATP production. Mitochondrial function inhibitors $MPP^+$ (1-methyl-4-phenylpyr-

Table 1

| | Unmedicated PD | Medicated PD | Healthy control |
|---|---|---|---|
| | n = 88 | n = 62 | n = 33 |
| Age in years [a] | 69.2 ± 9.6 | 67.3 ± 11.3 | 62.8 ± 7.7 |
| Male/female | 46/42 | 28/34 | 15/18 |
| Hoehn-Yahr [a] | 2.1 ± 0.9 | 2.7 ± 1.1 | — |
| Oxidized DJ-1 (ng/mg protein) [a] | 77 ± 66 ** | 49 ± 45 | 25 ± 9 |
| DJ-1 (ng/mg protein) [a] | 473 ± 146 | 512 ± 199 | 491 ± 166 |
| Ratio (Ox DJ-1/All DJ-1) | 0.163 | 0.096 | 0.051 |

Summary of research participants. [a] The mean values are shown with standard deviation. **P＜0.01 (Steel-Dwass, ANOVA) compared with medicated PD and healthy control. Significant difference between groups was only observed in oxidized DJ-1. (From Saito et al. (2016), and partially modified.) PD (Parkinson's disease)

idinium) and rotenone target mitochondrial electron transfer system enzyme complex I (Complex I).[16] Oxidative stress exposure damages Complex I, resulting in decreased ATP production and decreased membrane potential, resulting in mitochondrial damage and induction of cell death. Therefore, it was estimated that cytotoxicity was caused by over-oxidation of DJ-1 protein, which reduced the ability to eliminated ROS and caused neuronal cell death.

Thus, DJ-1 protein is considered to be able to eliminate produced ROS and to avoid mitochondrial injury. Not only mutant DJ-1 protein but also over-oxidized DJ-1 protein aggregate on mitochondria to form aggregates unique to neurodegenerative diseases, and it is revealed that electron transport system is inhibited to give cytotoxicity. Familial PD and sporadic PD are commonly observed in the insolubilized accumulation/aggregation of oxidized DJ-1 protein in the brain.[17]

## Potential of DJ-1 Protein as an Early Diagnosis and Clinical Diagnostic Criterion of PD

Le Naour et al. reported that DJ-1 protein was increased in the serum of breast cancer patients.[18] They revealed by isoelectric focusing analysis that extreme over-oxidized DJ-1 protein increased as brest cancer progressed. As mentioned above, it is suggested that the onset of PD and DJ-1 are closely related. Then, we analyzed the link between the clinical diagnostic criteria of PD and the qualitative and quantitative variation of DJ-1 protein in serum. Hohen–Yahr scale was well-known as PD clinical diagnostic indicators.[19, 20]

The Hohen-Yahr scale, which indicates the degree of progression of PD, as follows;

Stage 1: Unilateral involvement only.

Stage 2: Bilateral involvement without impairment of balance.

Stage 3: Mild to moderate bilateral disease

Stage 4: Severe disability; still able to walk or stand unassisted.

Stage 5: Wheelchair bound or bedridden unless aided.

We examined whether clinical diagnosis of DJ-1 protein in the serum of patients suspected of suffering from PD could make a definitive diagnosis at an early stage. With the cooperation of Yamanashi University Hospital, the amount of DJ-1 protein in the serum of 30 healthy persons and over 40 patients with PD at each stage was examined with MBL's CircuLex Human DJ-1/*PARK7* ELISA (enzyme-linked immune sorbent assay) Kit.

Unfortunately, an ELISA assay that measures the amount of DJ-1 protein was unable to find a significant difference in Stage 1 and Stage 2, which are early pathologies of PD. However a slight increase was observed only in patients with stage 3 or higher severity. This result cannot be used for early diagnosis of PD (Taira T. et al. 2011, unpublished data).

For this reason, quantitative variation of DJ-1 protein in serum could not be used as a diagnostic index in the early stage of PD.

The change of DJ-1 protein amount was inappropriate for the early clinical diagnostic index.

For two reasons, ELISA analysis was not suitable for early PD diagnosis.

1. Unlike breast cancer, PD has little variation in the amount of DJ-1 protein in the patient serum, and inherently there is a large amount of DJ-1 protein, so quantita-

tive changes cannot be determined.

2. The ELISA kit used could not distinguish between the reduced, oxidized, and extreme oxidized forms of DJ-1.

In conclusion, it was suggested that it appears not as a quantitative change in DJ-1, but as a variation in the ratio of reduced, oxidized, and over-oxidized forms. Therefore, it is necessary to analyze the fluctuation of the degree of oxidation of DJ-1 rather than the comparison of the absolute amount.

It is necessary to analyze IEF to compare the oxidation state of DJ-1. Compared to IEF and ELIZA, IEF is more complicated to operate, requiring specialized techniques and much time. Therefore, it is difficult to easily analyze many PD patient samples.

Therefore, it was investigated to quantify the excess oxidized form of DJ-1 by the ELISA method instead of quantifying all DJ-1 proteins. For this clinical diagnosis, it was necessary to develop an extreme oxidative DJ-1-specific antibody in which the 106th cysteine was sulfonylated. And this antibody needs to be available for the ELISA analysis.

## Development of Extreme Oxidized DJ-1-Specific Monoclonal Antibody and Its Application to Clinical Diagnosis

We tried to develop a monoclonal antibody against the synthetic peptide around the site where the 106th cysteine of the DJ-1 protein was sulfonylated. Unfortunately, we have not been able to develop extreme oxidized DJ-1 protein specific antibodies that can be applied to ELISA.

In 2009, the research group of Dr. Saito, who once belonged to our research group as a graduate student, succeeded in developing this specific antibody. And the antibody was also applicable to ELISA.[21)]

Dr. Saito and his collaborators carefully examined whether this specific antibody could be used for early PD clinical diagnosis by ELISA. As a result, Saito et al. Reported results as shown in Table 1.[22)]

The total amount of DJ-1 in the serum was in the range of 473 to 512 ng/mg protein among healthy controls, unmedicated PD patients, and medicated PD patient. On the other hand, the amount of extremely oxidized DJ-1 was increased about three times in unmedicated PD patients as compared with healthy controls. It was thought that over-oxidized DJ-1 increased with the severity of PD. However, surprisingly, Saito et al. revealed that the amount of oxidized DJ-1 decreased in medicated PD patients several years after PD onset compared to that in unmedicated PD patient.

These results suggested that extremely oxidized DJ-1 protein is involved in the early onset of PD. Furthermore, Saito et al. showed that in erythrocytes, the extremely oxidized DJ-1 protein was bound to multiple factors constituting the 20S proteasome. It has long been known that insoluble aggregated proteins accumulate in erythrocytes of PD patients in early onset. It is suggested that such aggregated proteins accumulate because extremely oxidative DJ-1 protein inhibits the function of 20S proteasome. These facts indicated that the DJ-1 protein is closely related to the onset and pathological condition of PD.

## Screening for Low-Molecular-Weight Compounds that Inhibit Extremely Oxidized DJ-1 Protein Formation

When exposed to excessive oxidative stress, the 106th cysteine of DJ-1 protein is preferentially converted to cysteine sulfonic acid. This conversion is cytotoxic and causes PD onset. Therefore, chemical compounds that specifically bind to this site are expected to suppress the formation of the extremely oxidized form of DJ-1. Moreover, these compounds can be expected to delay aggravation of PD and have a therapeutic effect PD. Therefore, we performed screening for low-molecular-weight compounds that can be orally administered as therapeutic agents for PD patients. The three-dimensional structure of the DJ-1 protein has already been clarified in detail. Based on this result, an in silico screening was performed to search for compounds that specifically bind to this specific site by a computer.[23, 24)]

We analyzed the specificity of binding between candidate compounds and DJ-1 in vitro using Quart crystal microbalance (Affinix Q). The candidate compounds were confirmed to bind specifically to the oxidation target site of DJ-1 protein. This compound suppressed cell death in SH-SY5Y cells exposed to hydrogen peroxide. In addition, we investigated whether this compound suppresses nerve damage caused by drugs in rats injected with drugs that induce PD.

These compounds prevented dopaminergic cell death in the substantia nigra and restored motor abnormalities in 6-hydroxydopamine-injected PD model rats. One mechanism of action of these compounds is the preven-

tion of excessive oxidation of DJ-1. Moreover, these compounds cross the blood-brain barrier in vitro. Taken together, the results show that these compounds should be basic drugs for PD therapy.

Furthermore, if this compound does not cause damage to each organ, improves chemical stability in the human body, and delivers to the target organ, this compound may be a new PD therapeutic agent.

## Conclusions

As I introduced in this issue, DJ-1 protein was isolated in the process of searching for binding partners of c-Myc protein. However, it was not a target c-Myc protein binding protein. The false clone that was not the subject of such original research was a new oncogene. In the focus formation assay that I routinely performed, the DJ-1 gene used by chance as a negative control had an unexpected function.

Louis Pasteur is known as the founder of modern bacteriology. As his affirmation, Chance favors the prepared mind (Le hasard ne favorise que les esprits préparés) is well known. I think that there was a researcher's mind that Pasteur said when I isolated the DJ-1 gene.

Twenty years have passed since the isolation of DJ-1 gene, but even now various functions of the DJ-1 protein remain to be clarified.

The following studies have been reported on the DJ-1 protein. DJ-1 protein has deglycase activity and suppresses the onset of PD,[25, 26] regulation of mitochondrial metabolism,[27] suppression of astrocyte inflammation,[28] suppression of myocardial apoptosis,[29] biomarker of invasive cholangiocarcinoma,[30] bone metabolism regulator.[31]

Before, I had missed the original purpose of the study because DJ-1 has so many different functions in various tissues and organs. However, I would like to continue research on DJ-1 protein as the responsibility of the person who isolated and identified DJ-1 protein and reported.

**Conflicts of interest:** None declared.

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