Redox-sensitive DJ-1 protein: an insight into physiological roles, secretion, and therapeutic target

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Graphical abstract

Abstract
The highly conserved DJ-1 protein fundamentally acts as a redox sensor conferring antioxidative cytoprotection under oxidative insults. DJ-1 preferentially undergoes oxidation at 106 cysteine residue (C106) under oxidative stress. Although initially identified as an oncogene, emerging evidence suggests the essential roles of DJ-1 in modulating numerous physiological processes involved in cellular growth, development, survival, and death. Compromised DJ-1 expression and function directly or indirectly trigger signaling cascades leading to pathophysiological conditions including neurodegeneration, cancer, stroke, and inflammatory diseases. Besides the intracellular functions, enhanced DJ-1 secretion into the extracellular fluid, including cerebrospinal fluid and blood, is related to Parkinson's disease (PD) and cancer pathogenesis. Here, we review the current knowledge regarding DJ-1's roles as a ubiquitous cytoprotective protein controlling numerous signaling pathways, secretion, and therapeutic potentials.

Key Words
- DJ-1
- oxidative stress
- antioxidative defense
- neurodegeneration
- therapeutic targets

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Introduction

The reactive oxygen species (ROS) are a group of hyperreactive molecular oxygen derivatives generated from regular metabolism through redox reactions or electronic excitation (Sies & Jones 2020). Growth factors and cytokines regulate ROS production, mediating crucial redox signaling pathways in a stable nanomolar range at normal physiological levels. For instance, hydrogen peroxide ($H_2O_2$) is the primary signaling entity that senses and regulates cellular metabolism and stress response, supporting homeostasis in response to stresses or other external perturbations (Ursini et al. 2016). However, increased formation and accumulation of ROS followed by a compromised antioxidant state leads to an unbalanced physiological oxidation phenomenon known as oxidative stress. Consistent oxidative stress leads to numerous disease manifestations characterized by non-specific posttranslational modifications and functional protein aggregation.

The DJ-1 (also called the DJ-1/PfpI, ThiJ/PfpI, or DJ-1/ThiJ/PfpI) superfamily is a highly conserved and diverse group of redox-sensitive proteins universally expressed in various organisms from humans to bacteria. In 1997, Nagakubo et al. identified DJ-1 protein as a novel oncogene promoting cell transformation in cooperation with the activated H-ras gene (Nagakubo et al. 1997). The PARK7/ DJ-1 gene encodes DJ-1 protein, and human DJ-1 is located on 1p36.23, notably expressed in tissues like the heart, skeletal muscle, kidney, brain, and testis. Human and mouse DJ-1 genes contain seven exons of 16–24 kb, where exons 2–6 encode DJ-1 protein. According to Taira et al., the promoter sequence for DJ-1 extends to a 2.1 kb area (−1015 to +1104) upward from the transcription start site (TSS) (Taira et al. 2001). In addition, two regulatory sequences, Sp-1 (−109 to −101 upstream from the TSS) (Taira et al. 2001) and X-box-binding protein-1S (−78 to −73 upstream from the TSS) (Duplan et al. 2013), have been discovered upregulating the expression of DJ-1 significantly. However, DJ-1 protein comprising 189 amino acid residues is highly conserved in diverse species from Archaea to Eukarya. Interestingly, this protein is more substantially expressed in reactive astrocytes than in the human brain neurons (Bandopadhyay et al. 2004), while both DJ-1 protein and mRNA are parallelly expressed in neurons, astrocytes, microglia, and oligodendrocytes in the mouse central nervous system (Bader et al. 2005).

DJ-1 is predominantly localized in the cytoplasm, whereas it expresses at low levels in the nucleus, mitochondria, and microsomes like the endoplasmic reticulum (ER) and Golgi apparatus (Bonifati et al. 2003, Miller et al. 2003, Canet-Avilés et al. 2004). Moreover, Usami et al. demonstrated that besides mitochondria and Golgi, DJ-1 directly associates with synaptic membranes (i.e. colocalizes with the synaptic vesicle proteins like synaptophyisin and Rab3A), implying novel DJ-1 roles in vesicular trafficking (Usami et al. 2011). However, stress conditions, including oxidative stress and UV B irradiation, lead to the intracellular redistribution of DJ-1, enhancing its translocation to the mitochondrial matrix and the intermembrane space, where DJ-1 might play roles in cellular defense mechanism (Canet-Avilés et al. 2004, Lev et al. 2008, Junn et al. 2009, Ren et al. 2011, Kim et al. 2012). Furthermore, Li et al. demonstrated that in response to diallyl disulfide treatment, DJ-1 translocates from the cytoplasm to the nucleus in human HL-60 leukemia cells, which might promote transcription of its target proteins responsible for cell differentiation (Li et al. 2016).

Under normal physiological conditions, wild-type DJ-1 forms homodimers; however, our group (Saito et al. 2016) and others reported DJ-1 associations with various proteins forming higher-order/high-molecular-weight (HMW) complexes. Choi et al. demonstrated six monomeric and four dimeric DJ-1 isoforms in the human brain (Choi et al. 2006). The appearance of isoforms and their participation in alternate complex HMW formations under oxidative stress may reflect distinct DJ-1 roles described in several pathophysiological conditions. Like other members of the DJ-1/PfpI superfamily, DJ-1 contains the ThiJ domain, which is structurally relevant to the type 1 glutamate amidotransferase domain (Lee et al. 2003). According to the structural studies, monomeric 19.8 kDa human DJ-1 protein represents a single flavodoxin-like Rossmann fold domain exhibiting a helix-strand-helix sandwich (a central six-stranded parallel $\beta$-sheet surrounded by eight $\alpha$-helices and with a $\beta$-hairpin on one end and a three-stranded antiparallel $\beta$-sheet on the opposite end) architecture with the conserved cysteine at position 106 (C106) in the nucleophile elbow pocket (Honbou et al. 2003, Huai et al. 2003, Wilson et al. 2003). Unlike the DJ-1/PfpI superfamily members, DJ-1 contains an additional C-terminal $\alpha$-helix masking the putative active site (i.e. C106) essential for the dimer interface (Wilson et al. 2003).

Human DJ-1 protein has three cysteine residues at positions 46, 53, and 106 (C46, C53, and C106, respectively), where C106 is highly sensitive to oxidative stress and arguably acts as a molecular switch for DJ-1 activity. However, one study demonstrated that instead of
C106, CS5 regulates DJ-1’s ROS quenching and chaperone activity (Shendelman et al. 2004). Besides three cysteine residues, other reported DJ-1 oxidation sites include methionine residues like M17, M26, M133, and M134 (Choi et al. 2006). Based on the general findings, C106 preferentially undergoes direct oxidation from thiolate (Cys-SH) to mono-oxidized DJ-1 sulfenate (Cys-SOH). Sequential oxidation of C106 produces oxidized DJ-1 (oxDJ-1) sulfinate (Cys-SO$_3$H) and over-oxDJ-1 sulfonate (Cys-SO$_2$H). In normal conditions, the sulfenate is transient and reversible to thiolate, thereby hardly affecting DJ-1 structure and regular functions. However, sulfinate and sulfonate are irreversible, affecting DJ-1’s overall structure, dimeric stability, and performance. Moreover, chemically unstable sulfinate is readily oxidized to sulfonate, resulting in aberrant DJ-1 aggregation with malfunctioning antioxidant, antiapoptotic, and cytoprotective actions. Interestingly, several studies suggested that adjacent amino acid residues of C106 give sulfinate and sulfonate more thermal stability than the sulfenate (Blackinton et al. 2009, Kiss et al. 2017).

Any loss or alteration (i.e. inactivation or overactivation) of DJ-1 activity leads to onsets of oxidative stress-related pathophysiological conditions. For instance, C106A and C104D (C106D oxidation-mimetic) mutations lead to the inactivation of DJ-1’s antioxidant activity in Drosophila (Meulener et al. 2006) and mitochondrial translocation even upon oxidative stress in vitro (Canet-Avilès et al. 2004). Missense mutations of C106 to serine, alanine, or aspartic acid harbor loss of DJ-1 antioxidant capacity (van der Pol et al. 2019), while the K130 mutation revokes entire DJ-1 functions, including ras-dependent transformation and anti-UV-induced apoptosis (Shinbo et al. 2006). Moreover, Parkinson’s disease (PD)-associated L166P and M26I homozygous mutants are associated with protein unfolding and reduced DJ-1 stability (Bonifati et al. 2004, Olzmann et al. 2004, Takahashi-Niki et al. 2004). We previously reported that oxDJ-1 and/or over-oxDJ-1 are found all over mice brains and in red blood cells and postmortem brain tissues of PD and PD with dementia patients, which seems to diminish with disease progression (Saito et al. 2014, 2016). We also prepared the oxDJ-1-specific primary antibody (Saito et al. 2014) and demonstrated the higher distribution of oxDJ-1 levels in PD-related sites such as the brain, heart, and skeletal muscle than in peripheral tissues (Mita et al. 2018). On the other side, DJ-1 is overexpressed in malignant cells and tissues, providing antioxidative defense against the natural cell-killing activity of ROS, leading to uncontrolled cell proliferation (Nagakubo et al. 1997, Ariga 2015).

Besides having versatile intracellular functions, DJ-1 mediates crucial physiological and pathophysiological roles when secreted into the extracellular space. Microdomain-mediated secretion of DJ-1, induced by oxidation at C106, has been reported in HeLa cells cultured in serum-free conditions (Tsuboi et al. 2008). Moreover, increased levels of secreted DJ-1, for example, into serum, plasma, and cerebrospinal fluid have been observed in patients with sepsis (Amatullah et al. 2017), breast cancer (Tsuchiya et al. 2012), strokes (Aleyasin et al. 2007), melanoma (Pardo et al. 2006), allergic responses (Kim et al. 2013a), multiple sclerosis (MS) (Hirotani et al. 2008), and early phases of PD (Waragai et al. 2007). Nonetheless, reduced levels of DJ-1 and increased ROS levels are found in atopic dermatitis patients compared with healthy volunteers, in which alterations are unrelated to disease severity (Kim et al. 2013a). In the case of newly diagnosed breast cancer patients, a higher level of DJ-1 in serum (Le Naour et al. 2001) and nipple fluid (Oda et al. 2012) has been reported. However, one study demonstrated that although DJ-1 mRNA was upregulated in breast cancer, DJ-1 protein expression was lower (Kawate et al. 2013). These results may justify the different DJ-1 transcription, translation, and secretion levels in cancer cells. The implication of DJ-1 secretion in the etiology and progression of these diseases implies the potential roles of DJ-1 as a biomarker influential for the diagnosis, monitoring, and prognosis (Zhang et al. 2020b).

We reported that secretion of DJ-1, when induced by a neurotoxin 6-hydroxydopamine (6-OHDA), relies on an autophagy-based unconventional secretion pattern in human neuroblastoma SH-SYSY cells and mouse embryonic fibroblast (MEF) cells (Urano et al. 2018). Treatment of experimental cells with 6-OHDA decreases glutathione levels, thereby inducing secretory autophagy through mTOR-independent activation of AMP-activated protein kinase (AMPK) and its downstream effector unc-51 like autophagy activating kinase 1 (ULK1). In addition, several autophagy-related proteins like ATG5, ATG9, and ATG16L1, governing autophagic membrane biogenesis, were involved in this secretion process. Interestingly, 6-OHDA-simulated oxidative insult was independent of C106 oxidation. The ongoing research is focused on unveiling the basic understanding regarding DJ-1 secretion, like the pathway of DJ-1 translocation, cellular machinery recognizing DJ-1 as a leaderless protein, determination of the fate between degradative and secretory autophagy, and membrane proteins mediating fusion of DJ-1 carriers with the plasma membrane, if it exists.
In the last two decades, DJ-1 modulating different signaling cascades and coordinating distinct adaptative cellular actions (discussed later in this review) under physiological and pathophysiological conditions have been revealed. Furthermore, potential links between DJ-1 and several oxidative stress-induced pathophysiological conditions (discussed later in this review) have been established. Therefore, this review focused on the relevant roles of redox-sensitive DJ-1 in several pathophysiological conditions and discussed its use as a potential therapeutic target.

Physiological roles of DJ-1

DJ-1 is a multifunctional protein orchestrating distinct physiological processes, including antioxidative defense, apoptosis, signal transduction, fertilization, transcriptional regulation, autophagy, and protein repair (Cao et al. 2015, Ariga & Iguchi-Ariga 2017, Zhang et al. 2020a, Mencke et al. 2021). However, its role as an oxidative stress regulator, particularly in the upregulation of pro-survival signaling pathways in brain cells, is most comprehensively studied and considered its principal function. The Cys106 residue and its oxidation, in particular, the sulfinate form, have been reported to be essential for exhibiting DJ-1’s cytoprotective functions, including ROS modulation, DJ-1 translocation to and protection of mitochondria, inhibition of α-synuclein fibrillation, and low-molecular-weight aldehyde detoxification while overoxidation leads to a loss of biological function (Canet-Avilés et al. 2004, Blackinton et al. 2009, Wilson 2011).

Antioxidant activity

The antioxidative activity of DJ-1 is synchronized by cellular levels of ROS mainly produced in mitochondria during regular oxidative phosphorylation. The enhanced translocation of DJ-1 to the mitochondria under oxidative stress maintains mitochondrial homeostasis (Canet-Avilés et al. 2004, Blackinton et al. 2009, Junn et al. 2009), although several studies encountered any relationship between oxidative stress and DJ-1 exportation to mitochondria (Zhang et al. 2005, Osuagwu et al. 2019). However, as a redox-sensitive chaperone, DJ-1 is upregulated in response to oxidative insult performing as a cellular feedback mechanism to confer antioxidative defense (Fig. 1).

DJ-1 can directly quench ROS like H$_2$O$_2$ via self-oxidation at Cys-106 (Taira et al. 2004). However, this non-enzymatic ROS neutralization is insufficient compared to other antioxidative enzymes (e.g. peroxiredoxins (PRXs), glutathione peroxidase, and catalase) in exhibiting robust cytoprotection (Taira et al. 2004, Junn et al. 2005). Under oxidative stress, DJ-1 upregulates the expression of rate-limiting enzymes in glutathione synthesis, namely glutamate-cysteine ligase modifier (GCLM) and catalysis (GCLC), heat shock protein, and uncoupling proteins leading to the protection of dopaminergic neurons through controlling ROS formation (Guzman et al. 2006, Osuagwu et al. 2009). Moreover, DJ-1 upregulates the Akt-PI3K signal cascade is still elusive; however, increasing reports suggest that as a positive upstream regulator, proper DJ-1 function is essential for Akt phosphorylation to confer mitochondrial quality control under oxidative stress, thereby defending dopaminergic neuronal degeneration (Aleyasin et al. 2010, Zhang et al. 2016). Phosphorylation of Akt activates the redox-related master transcription regulator NF-E2-related factor 2 (Nrf2). DJ-1 stabilizes Nrf2 activity by inhibiting the association of Nrf2 with its negative regulator Kelch-like ECH-associated protein 1 (Keap1) and subsequent ubiquitination (Clements et al. 2006). Moreover, DJ-1 facilitates nuclear translocation of Nrf2, resulting in its binding to ARE, thereby stimulating the expression of its downstream target antioxidant enzyme genes, including GCLM, GCLC, SOD1, heme oxygenase-1 (HO-1), NAD(P)H quinone oxidoreductase 1 (NQO-1), and thioredoxin reductase, involved in crucial antioxidant defense (Clements et al. 2006, Im et al. 2012, Zhang et al. 2016, 2019). Members of the NADPH oxidase (NOX) family enzymes like NOX4 are predominantly responsible for cytosolic ROS production. As a negative ROS regulator, loss of DJ-1 or siRNA-mediated DJ-1 silencing augmented ROS generation and NOX4 expression in renal proximal tubule cells (Cuevas et al. 2015) and reduced levels of Nrf2-dependent antioxidants in chronic obstructive pulmonary patients (Malhotra et al. 2008). Consistent with these observations, Im et al. reported that WT DJ-1, but not the pathogenic mutant isoforms L166P and M26I, upregulates the Nrf2-mediated transcriptional expression of thioredoxin 1 (Trx1) (Im et al. 2012). Trx1 is an antioxidant protein that acts as a potent survival factor by protecting cells from oxidative stress (Umeda-Kameyama et al. 2007).
and regulating the apoptosis signal-regulating kinase-1 (ASK1) activity (Saitoh 1998). Nonetheless, it was found that Nrf2 activation and Nrf2-ARE-mediated antioxidant gene expression are independent of DJ-1 signaling in the brain or brain-derived primary cultures (Gan et al. 2010). These results suggest that the involvement of DJ-1 in Nrf2-regulated antioxidative cytoprotection is distinct in different cell types.

DJ-1, as an upstream regulator of the extracellular signal-regulated kinase 1/2 (ERK1/2) cascade, is upregulated under oxidative insults (Lev et al. 2009), stimulating ERK1/2 phosphorylation (Gu et al. 2009) or repressing its inhibitor, dual-specificity phosphatase 1 (DUSP1)'s expression (Kato et al. 2013) to confer antioxidant response. Furthermore, DJ-1 interaction with ERK1/2 ensures nuclear translocation leading to ETS-domain protein (Elk1) stimulation followed by upregulated SOD1 expression to manage oxidative insults (Wang et al. 2011).

DJ-1's antioxidative properties can also be described by showing its roles in preventing mitochondrial dysfunction (i.e. loss of mitochondrial membrane potential and ATP production and rise in mitochondrial ROS generation). DJ-1-mediated Nrf2 activation retains regular mitochondrial bioenergetics, including NADPH generation (Clements et al. 2006, Holmström et al. 2013). Likewise, DJ-1 regulation of the Keap1/Nrf2 pathway stimulates mitochondrial isocitrate dehydrogenase synthesis that represses intracellular and mitochondrial ROS levels, thereby maintaining mitochondrial integrity (Yang et al. 2017a). Upon oxidative stress, DJ-1 binding with mitochondrial complex I promotes ROS scavenging activity (Hayashi et al. 2009) while binding with ATP synthase β subunit (as a chaperone) represses mitochondrial uncoupling and enhances ATP production (Chen et al. 2019). Furthermore, in cultured dopaminergic cells, DJ-1 overexpression improves ATP production, mitochondrial mass, and complex I activity (Zhang et al. 2016). In addition, oxDJ-1 enhances proteasomal degradation of mitochondrial fission and fragmentation protein Fis1 via Akt signaling (Zhang et al. 2012).

**Regulation of protein synthesis**

DJ-1 impacts protein synthesis and expression stages, including transcription, translation, ribonucleoprotein complex formation, and ribosome assembly. Structural analyses suggest a lack of classical RNA binding motifs in DJ-1. However, oxidation-dependent non-classical
direct DJ-1 interaction with GG/CC-rich sequences of several mRNA targets, including glutathione peroxidases, mitochondrial proteins, and PTEN/Akt pathway effectors, affecting their expression in neuroblastomacell lines, mouse brain, and PD patient brains, has been reported (van der Brug et al. 2008, Blackinton et al. 2009). Moreover, DJ-1 can form HMW complexes that regulate crucial physiological functions, including ubiquitin-proteasome-mediated protein turnover, α-synuclein accumulation inhibition, and RNA-mediated gene regulation (Shendelman et al. 2004, Jin et al. 2007, Xiong et al. 2009, Saito et al. 2016, Piston et al. 2017). Determined by the oxidation status, DJ-1 has been shown to form specific HMW complex compositions with proteins involved in RNA processing, including heterogeneous ribonucleoproteins A1, A2B1, and CIC2 and glycolysis, which stabilizes and protects mRNAs in the human brain and cultured neuroblastoma cells (Piston et al. 2018). Indeed, loss of DJ-1 function resulted in transcriptional dysregulation of genes essential for catecholamine homeostasis in neuroblastoma cells (Piston et al. 2017, 2018).

As a coactivator or corepressor, DJ-1 directly or indirectly binds to several transcription factors to regulate the transcriptional activity of their target genes, affecting various cellular functions, including dopamine synthesis, response to oxidative stress, and signaling pathways. DJ-1-regulating transcription factors and their modified products, including Nrf2, p53, polypyrimidine tract-binding protein-associated splicing factor (PSF), sterol regulatory element-binding protein, Ras-responsive element-binding protein, signal transducer and activator of transcription 1 (STAT1), androgen receptor (AR) and its regulatory proteins, Keap1, Nrf2, nuclear receptor-related 1 protein (Nurr1), Elk1, nuclear factor-kappa B (NF-xB), and cAMP-response-element-binding protein 1 (CREB1) have been comprehensively reviewed (Takahashi-Niki et al. 2017, Huang & Chen 2021). For instance, DJ-1 positively regulates the AR transcriptional activity by sequestering AR transcriptional inhibitors like protein inhibitor of activated STAT (Takahashi et al. 2001) and DJ-1-binding protein (Niki et al. 2003), which are essential for male reproductive system development and maintenance. Likewise, DJ-1 inhibits the sumoylation of PSF, which represses tyrosine hydroxylase (TH) gene transcription (Zhong et al. 2006) and sequesters PSF from the human TH gene promoter (Ishikawa et al. 2010) to upregulate dopamine synthesis in human. DJ-1 also directly interacts with the tumor suppressors, p53 (Fan et al. 2008, Takahashi-Niki et al. 2016), PTEN, and PTEN-induced kinase 1 (PINK1) transcription factor forkhead box O3a (Kim et al. 2009), to downregulate their transcriptional activity resulting in the development of cancers.

Overexpression of WT DJ-1 or L166P mutant enhances tunicamycin-stimulated acute ER stress by upregulating mRNA and protein levels of activating transcription factor 4 (ATF4) and its downstream effector proteins like CHOP and Bip (Yang et al. 2019). Here, DJ-1 directly binds and stabilizes ATF4, eventually accelerating neuronal death in mice. Indeed, this study demonstrated a counter role of DJ-1 in inducing cell death under ER stress conditions rather than ensuring cell survival reported commonly under oxidative stress. This disagreement demands further research to clarify the context-dependent regulatory roles of DJ-1 in response to distinct survival challenges.

**Enzymatic functions**

DJ-1 in dopaminergic cells exhibits enhanced cytoprotective activity through its proteolytic conversion into an active protease. Synthesized as a latent zymogen, dopaminergic DJ-1 undergoes a C-terminal 15-amino acid peptide cleavage under mild oxidative-challenged conditions. This proteolytically transformed DJ-1 is highly similar in sequence to bacterial PfpI protease family and heat shock protein 31 and acts as a cysteine protease with 26-fold higher catalytic activity than the WT (Chen et al. 2010, Mitsugi et al. 2013). Although any yet unknown protease mediates this activation is elusive, activated protease boosts cytoprotection against oxidative stress-induced apoptosis (Chen et al. 2010). This hyperactive DJ-1 forms a caspase-like catalytic dyad between the highly conserved C106 and a nearby histidine (H126) for catalysis. Several reports demonstrated low protease activity of DJ-1 (Olzmann et al. 2004, Koide-Yoshida et al. 2007, Chen et al. 2010), although the recognition sequence of DJ-1 protease has not been reported. However, the optimal pH for DJ-1 protease activity is around 6, which decreases at higher alkaline conditions, implying that DJ-1 protease might work in some organelles like the endosome, lysosome, Golgi apparatus, and synaptic vesicle or locally created oxidative stress-induced acidic regions where lower pH is maintained (Mitsugi et al. 2013). The C106A mutation that turns DJ-1 unable to become oxidized prohibits cytoprotective protease function of both wild and cleaved DJ-1 (Chen et al. 2010, Mitsugi et al. 2013).

DJ-1 acts as an antiglycative agent to repair methylglyoxal (MGO)- and glyoxal-glycated proteins (Richarme et al. 2015) and nucleic acids (Richarme et al. 2006).
As a deglycase, DJ-1 alleviates MGO toxicity, Nε-carboxymethyl-lysine-linked α-synuclein glycation, and intracellular α-synuclein aggregation (Sharma et al. 2019). Furthermore, DJ-1 overexpressing tumor cells exhibit intense histone glycation that can counterattack MGO-induced cell death even at high doses. These results support DJ-1’s function as a histone deglycase in maintaining chromatin dynamics by rescuing MGO-induced posttranslational modifications (Galligan et al. 2018, Zheng et al. 2019). However, one study demonstrated that DJ-1 neither possesses any deglycase activity nor shields cells from acute MGO toxicity; instead, it acts as glutathione (GSH)-independent glyoxalase (Andreeva et al. 2019). DJ-1’s glyoxalase activity in quenching reactive carbonyl species to protect against glyoxal-induced Caenorhabditis elegans death has been previously reported (Lee et al. 2012). Among others, DJ-1 activities as an intrinsic redox-sensitive cysteine esterase (Vázquez-Mayorga et al. 2016), low-molecular thiols detoxifier (Matsuda et al. 2017), and atypical PRX-like peroxidase in scavenging cytokine-induced H$_2$O$_2$ in mice (Andres-Mateos et al. 2007) in conferring cytoprotection are evident.

**Apoptotic cell death**

DJ-1 plays a fundamental role in dealing with oxidative stress-induced apoptotic cell death (Fig. 2). DJ-1 has been shown to modulate miR-221 (miRNAs in the human brain, upgrading neurite extension and neuronal differentiation) expression in part by regulating the mitogen-activated protein kinase (MAPK)-ERK pathway. DJ-1 positively regulates miR-221 expression, resulting in transcriptional suppression of many pro-apoptotic proteins, including bcl-2-like protein 11, bcl2 modifying factor, and bcl2 interacting protein 3-like, which safeguards 1-methyl-4-phenylpyridinium (MPP$^+$)-induced dopaminergic neuronal cell death (Oh et al. 2018). It has been reported that DJ-1 can regulate signal transduction of MAPKK kinase ASK1, a redox sensor that mediates crucial roles in stress-induced apoptosis, cell differentiation, and survival (Cao et al. 2014). Under physiological conditions, the antioxidant protein Trx1 physically binds to ASK1 to repress its activation, whereas oxidative stress leads the oxidized Trx1 to escape from the ASK1-Trx1 complex, activating the c-Jun NH2 terminal kinase (JNK) and p38 signaling cascade. Depending on the ROS levels, DJ-1 directly interacts with ASK1 and negatively regulates its activation by dislocating ASK1 homodimerization leading to its structural instability (Mo et al. 2008, Waak et al. 2009).

Moreover, oxDJ-1, but not over-oxDJ-1, can sequester ASK1 to its static configuration (Junn et al. 2005, Cao et al. 2014). DJ-1 also elevates intracellular Trx1 levels through the Nrf2 pathway (Im et al. 2012) that compacts the Trx1-ASK1 inhibitory complex (Im et al. 2010). In addition, DJ-1 interacts directly with homeodomain-interacting protein kinase 1 (HIPK1) to control the death-associated protein kinase 1 (HIPK1) to control the death-associated protein 6 (Daxx6)-ASK1 pathway (Sekito et al. 2006) and hinders cytoplasmic translocation of Daxx6 arresting its effector kinase ASK1 activation (Junn et al. 2005, Karunakaran et al. 2007). However, under the intensive oxidative challenge, for example, by increasing doses of N-(4-hydroxyphenyl) retinamide (4-HPR), the DJ-1-ASK1-Trx1 complex dissociates, releasing ASK1 to activate p38 leading to apoptosis initiation (Cao et al. 2014). Oxidative insults and CI06 oxidation are essential in promoting the direct interaction of DJ-1 with ASK1 as the C106A mutation fails to repress ASK1 activation (Waak et al. 2009).

DJ-1 protects cells from tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced apoptosis by hindering pro-caspase-8 activation (Fu et al. 2012). DJ-1’s interference with Fas-associated protein death domain binding to pro-caspase-8 represses active caspase-8 generation leading to impaired death-inducing signaling complex formation. On the other hand, the L166P mutant cannot protect cells from TRAIL-induced apoptosis (Fu et al. 2012). Moreover, DJ-1 downregulates the transcriptional activity of tumor suppressor p53 through direct binding with Sirtuin family protein 1 (Takahashi-Niki et al. 2016) or controls p53 transcription-mediated Bax-caspase signaling to resist cells from committing apoptosis (Fan et al. 2008). Recently, a study reported that DJ-1 suppresses p53 expression in intestinal epithelial cells to prevent mice colitis inflammation and apoptosis (Zhang et al. 2020). Besides, DJ-1’s role in ERK-dependent mitophagy protects dopaminergic neurons from rotenone-induced apoptosis (Gao et al. 2012).

Under limited oxygen concentrations, DJ-1 as an upstream activator and stabilizer of hypoxia-inducible factor-1α (HIF-1α) protects cancer cells (e.g. U2OS cells and transformed MEF) from hypoxia-induced apoptosis (Vasseur et al. 2009). Parsanejad et al. reported that DJ-1 negatively regulates the Von Hippel Lindau (VHL) protein ubiquitination activity by inhibiting HIF-VHL interaction since the loss of DJ-1 decreases HIF-1α protein (but not HIF1-α mRNA) levels in both hypoxia and oxidative stress neuronal cell models (Parsanejad et al. 2014). Moreover, it has been reported that the coexpression of DJ-1 and HIF-1α promotes colorectal cancer cell survival under hypoxia via upregulating...
the PI3K/Akt pathway (Zheng et al. 2018). Under UV irradiation, DJ-1 negatively regulates the MEKK1-SEK1-JNK1 signaling cascade to protect against UV-induced cell death (Mo et al. 2008). The WT/thiolate DJ-1 blocks the UV-induced nuclear translocation of MEKK1 via its cytoplasmic sequestration, leading to the suppression of downstream activation of SEK1 and JNK1. Moreover, oxDJ-1 counteracts the early stages of α-synuclein nucleation and elongation as a chaperone. However, the oxDJ-1 remodels mature α-synuclein fibrils to produce diverse toxic oligomeric species leading to the induction of apoptotic cell death (Kumar et al. 2019). Interestingly, this study demonstrated the detrimental mechanism of DJ-1’s chaperone function. Therefore, DJ-1 appears to regulate apoptotic cell death through different mechanisms under distinct stress conditions.

**Autophagy**

Autophagy/macroautophagy is an evolutionary conserved cellular self-eating process that, under nutrient stress and at critical developmental points, contributes to nutrient recycling and cellular defense by lysosomal digesting of unnecessary and dysfunctional cellular components, including damaged and redundant organelles and invading pathogens (Jiang et al. 2013). Emerging evidence suggests DJ-1’s ambiguous roles in promoting (González-Polo et al. 2009, Gao et al. 2012) or inhibiting (Ircher et al. 2010, Thomas et al. 2011, Jaramillo-Gómez et al. 2015) oxidative insult-induced autophagy based on pathophysiological conditions like PD and cancers (Ren et al. 2010, Tsoporis et al. 2021). Likewise stated earlier, DJ-1’s responsibility, particularly whether to choose pro-survival autophagy or
apoptotic death, is determined by the severity of oxidative insults (Fig. 2). This phenomenon is ideally reported in a study where DJ-1 responded differently to distinct 4-HPR-induced ROS levels: mild oxidative stress led DJ-1 to bind with ASK1 tightly, conferring autophagy-based viability while over-oxDJ-1 sets ASK1 free to initiate p38-activated apoptotic death (Cao et al. 2014).

DJ-1 overexpressed cell lines, including HeLa, HEK293, and human adenocarcinoma A549, exhibited suppressed conversion of microtubule-associated protein light chain 3 (LC3) I to II (LC3-II, a standard autophagosome marker) leading to inhibition of autophagic flux, resulting in increased levels of Beclin1 (a critical regulator of autophagy and cell death) and LC3-associated protein p62 (Ren et al. 2010). Autophagy studies using DJ-1-deficient MEF cells reported lower LC3-II and p62 levels than WT MEF cells. Treating the DJ-1-deficient MEF cells with autophagy blocker Bafilomycin A1 (Irlicher et al. 2010) or lysosomal protease inhibitors (Krebiehl et al. 2010) restored both LC3-II and p62 levels, suggesting that DJ-1 deficiency upregulates autophagic degradation. These results support the finding that DJ-1 is highly expressed in carcinoma, where autophagy is repressed to promote tumorigenesis or DJ-1 deficiency enhances autophagic activity. So far, DJ-1 regulates basal autophagy through several mechanisms, including modulation of JNK-Beclin1 (Ren et al. 2010), ERK1/2 (Krebiehl et al. 2010, Gao et al. 2012), and PTEN/P13K/Akt/mTOR (Jaramillo-Gómez et al. 2015) signaling pathways. The proof of DJ-1 interfering with mTOR signaling pathways to control autophagy can describe the phenomena of protein accumulation and autophagic impairment in PD and other neurodegenerative diseases (NDs).

Chaperone-mediated autophagy deals with the heat shock protein A8-mediated KFERQ motif-based selection and direct lysosomal delivery of substrates transported by the lysosomal-associated membrane protein 2A (LAMP2A). Xu et al. reported that DJ-1 deficiency represses mild α-synuclein-induced LAMP2A upregulation and enhances lysosomal LAMP2A degradation leading to α-synuclein accumulation in SH-SYSY cells and PD mice models (Xu et al. 2017). However, Nash et al. did not find any significant consequence of α-synuclein uptake and clearance in DJ-1-deficient microglia (Nash et al. 2017). These discrepancies can be discussed by divergent roles and regulation of DJ-1 in different cell lines under distinct conditions. To sum up, the roles of DJ-1 in controlling autophagy are distinct, either detrimental or beneficial, based on the experimental conditions that demand further studies to employ the current findings in therapeutic applications.

Therapeutic targets
The ability of DJ-1 to protect cells from oxidative stress and act as a direct or indirect modulator of several physiological cytoprotective functions made it an exciting target in designing therapeutic interventions.

Neurodegenerative disorders
NDs, including PD, Alzheimer’s disease (AD), Huntington’s disease (HD), amyotrophic lateral sclerosis (ALS), dementia with Lewy body (DLB), and MS, result from neuronal dysfunctions caused by the gradual loss of specific neuronal cells. Studies on genetic defects leading to abnormal regulation of corresponding proteins revealed the existence of standard features, including pathologic pathways and disease progression mechanisms, shared by different NDs. For instance, oxidative stress, mitochondrial dysfunction, atypical protein aggregation, irregular apoptosis and autophagy signaling, and neuroinflammation are shared by NDs. Although initially discovered as the causative agent of familial PD, altered expression and atypical DJ-1 function leading to compromised downstream mechanisms have been implicated in most NDs. In addition, the interaction of DJ-1 with some other proteins like α-synuclein in PD, amyloid-β and tau in AD, and SOD1 and TAR DNA binding protein-43 (TDP-43) in ALS and HD has been revealed. DJ-1 has been widely studied as a prospective therapeutic target for PD and has been reviewed recently (Repici & Giorgini 2019, Huang & Chen 2021). Lower DJ-1 protein levels and loss of DJ-1 function mutations, including deletion of exon 1–5 (Bonifati et al. 2003), L166P (Bonifati et al. 2003), M261 (Abou-Sleiman et al. 2003), E64D (Hering et al. 2004), and L172Q (Taipa et al. 2016), have been reported in dopamine neuron degeneration in autosomal recessive inherited PD. Unfortunately, current knowledge regarding how DJ-1 protects against and is regulated in NDs other than PD is minimal. However, based on the generalized roles of DJ-1 in shared neurodegenerative pathways, DJ-1 might employ therapeutic effects in other NDs as well.

The relevant studies suggest two DJ-1-based therapeutic strategies: increasing DJ-1 levels by delivering recombinant DJ-1 and blocking DJ-1 overoxidation by DJ-1-binding compounds. Several reports demonstrated that intranigrally or intrastriatally injected DJ-1 delivery could protect dopaminergic neuron loss and lessen associated motor behavior defects in mice/rat PD models (Inden et al. 2006, Gao et al. 2012, Sun et al. 2012, Batelli et al. 2015, Lev et al. 2015). Moreover, increasing DJ-1 activity by delivering recombinant HIV trans-activator...
of transcription protein (TAT)-DJ-1 and ND-13 (a conjugation of 13 and 7 amino acids of DJ-1 and TAT, respectively) has been tested (Antoniou & Borsello 2010, Kim et al. 2014, Batelli et al. 2015, Molcho et al. 2018). The recombinant HIV-derived TAT cell permeable peptide-fused DJ-1 protein can be delivered to all tissues, including the CNS. Batelli et al. reported that TAT-DJ-1, when administered intrastriatally, restored dopamine reduction in vivo with reduced 6-OHDA toxicity (Batelli et al. 2015). In addition, ND-13 delivery lessened dopaminergic dysfunction and improved motor behavior in a 6-OHDA-treated hemiparkinsonism mouse model (Lev et al. 2015), conferred neuroprotection in an MS mouse model (Glat et al. 2016), and improved ventral horn ischemic damage of the spinal cord in an ischemia–reperfusion (I/R) rabbit model (Kim et al. 2014) and ischemic injury in an I/R mouse model (Molcho et al. 2018).

The second therapeutic strategy targeting DJ-1 implies the inhibition of over-oxidation of DJ-1 leading to the loss of DJ-1 function. Several DJ-1-binding compounds capable of maintaining the active/oxidative form and restoring/increasing the DJ-1 level that was lost due to oxidative stress and genetic defect might have different downstream effects; thus, it also warrants testing these strategies in mutation/genetic defect-induced ND models. As the current knowledge regarding the involvement of DJ-1 in NDs aside from PD is insignificant, it will also be interesting to investigate the therapeutic efficacy of the strategies stated earlier.

**Cancer**

DJ-1 activity is upregulated in carcinoma, and a correlation between hyper DJ-1 activity and cancer progression has been revealed, which might be responsible for poor survival outcomes and resistance to chemotherapy. Positive DJ-1 regulation of several pathways, including Akt/mTOR, MEK/ERK, Wnt, and NF-κB signaling, or downregulation of JNK, p53, and ASK1 signaling support tumor initiation, uncontrolled proliferation, and metastasis (Davidson et al. 2008, Sitaram et al. 2009, He et al. 2012, Zheng et al. 2019, Li et al. 2020). Moreover, increased secretion of DJ-1 in plasma, serum, and nipple fluid has been reported in the pathophysiology of breast cancer and melanoma (Le Naour et al. 2001, Pardo et al. 2006, Oda et al. 2012, Tsuchiya et al. 2012, Ariga & Iguchi-Ariga 2017). Therefore, the intervention of the tumor protection function of DJ-1 may be employed to inhibit cancer initiation and progression.

Downregulation of DJ-1 expression can suppress cancer cell migration and invasion in pancreatic ductal adenocarcinoma cells and block metastasis in mice by interfering with the SRC/ERK/urokinase plasminogen activator (uPA) pathway (He et al. 2012). Other studies demonstrated that RNA interference (RNAi)-based knockdown of DJ-1 rendered tumor cells sensitive to different chemotherapeutic agents, including gemcitabine in pancreatic cancer (Chen et al. 2012) and taxol and cisplatin in non-small cell lung cancer (Zeng et al. 2011). Several other potential chemotherapeutic agents evaluated in the DJ-1 knockdown condition include 4-HPR (Cao et al. 2014), dihydroartemisinin (Zhu et al. 2014), and TRAIL/Apo-2L (Hod 2004).

Using the in silico modeling, Maksimovic et al. recently reported DJ-1’s deglycase activity-oriented small library of prospective DJ-1 inhibitors that warrants further in vitro and in vivo investigation for their efficacy in suppressing DJ-1’s deglycase activity to control carcinoma (Maksimovic et al. 2020).
et al. 2021). As a natural product, Ashwagandha can downregulate DJ-1 expression in a preclinical model of ovarian cancer that blocks ovarian cancer metastasis (Gupta et al. 2014). The synthetic antifungal agent ciclopirox olamine has been reported to downregulate DJ-1 expression leading to mitochondrial dysfunction and ROS accumulation, thereby inhibiting colorectal cancer growth (Zhou et al. 2019). Furthermore, diallyl disulfide reduced DJ-1 expression that suppresses the Src pathway, leading to induction of apoptosis and inhibition of metastasis potential of leukemia cells (Liu et al. 2018). In addition, the DJ-1 suppression efficacy of paclitaxel leads to the inhibition of breast cancer metastasis (Ismail et al. 2018), and the transformation of NIH3T3 cells (MacKeigan et al. 2003) has been evaluated.

The siRNA-based therapeutics are practically far from clinical applications; thus, designing small molecular compounds interfering with DJ-1’s cytoprotecting activity may improve the efficacy of the chemotherapeutics mentioned earlier (Jin 2020). Furthermore, pharmaceutical compounds interfere with DJ-1 homodimerization; destabilizing DJ-1 structure and promoting ubiquitin-proteasome-based DJ-1 degradation might be therapeutically attractive to inhibit DJ-1 overexpression in carcinoma.

Sepsis-induced immunosuppression

Sepsis is one of the leading causes of global intensive care unit death, characterized by uncontrolled extravagant inflammation and compromised immune reaction leading to distant multiorgan damage or failure (Hotchkiss & Opal 2010). Considering the crucial roles of ROS in modulating inflammatory responses and triggering DJ-1-mediated cytoprotection, several studies unveiled the contribution of DJ-1 in sepsis-induced immunosuppression.

Physiological ROS levels trigger several DJ-1-mediated signaling cascades conferring cytoprotection by regulating inflammatory response and improving macrophage-led bactericidal activity. For example, direct DJ-1 interaction with p47phox, a subunit of NOX, facilitates NOX-related ROS generation promoting pro-inflammatory cytokine discharge in early active macrophages (Liu et al. 2015). Moreover, overexpression of DJ-1 triggers NOX activation that restores impaired macrophage activity and prolongs the life expectancy of lipopolysaccharide (LPS)-treated DJ-1 knockout mice by reducing bacterial burdens. Similarly, cytoprotective functions of DJ-1 in defending sterile LPS-induced acute lung injury and ventilator-induced lung injury propelled by intense oxidative stress have been reported (Amatullah et al. 2021). Conversely, another study by the same group showed improved mortality and bacterial clearance in organs and blood of DJ-1 deficient cecal ligation and puncture-mice model (Amatullah et al. 2017). This study demonstrated that DJ-1-p47phox binding interrupts NOX complex stability, promoting Nox2 (gp91phox) ubiquitynlated degradation in stimulated bone marrow macrophages. This DJ-1 action reduces optimal ROS generation crucial for macrophage M1 differentiation and bacteria-killing activities leading to compromised clinical sepsis consequences. Interestingly, both experiments found DJ-1 as a negative regulator of pro-inflammatory cytokine production. The paradoxical outcomes in both sepsis mice models demand further studies to clarify the contradictory pathophysiological roles of DJ-1 in mediating inflammation and bacterial clearance in distinct hosts under unique experimental settings.

Myocardial I/R injury

Myocardial I/R injury is the principal severity factor in ischemic heart disease induced by oxidative stress. Several in vivo studies reported that downregulation of DJ-1 results in increased sensitivity to ischemia and enlarged infarct size in the brain (Aleyasin et al. 2007, Yang et al. 2017b, Molcho et al. 2018, Peng et al. 2019) and heart (Dongworth et al. 2014, Shimizu et al. 2016). Billia et al. reported DJ-1’s antioxidative roles in protecting the murine heart in vivo from oxidative damage (Billia et al. 2013). Similar cardioprotective functions of DJ-1 in I/R-induced cell lines, for example, H9c2 rat myoblasts (Yu et al. 2013) and HL-1 cardiac cells (Dongworth et al. 2014), are evident as well. Shimizu et al. demonstrated proteolytic DJ-1 cleavage in response to acute myocardial I/R injury that can attenuate heart failure by regulating mitochondrial fission (Shimizu et al. 2016) and reducing glycative stress (Shimizu et al. 2020) in mice. The later study discovered a novel contribution of DJ-1 in protecting at least two mitochondrial components (e.g. complex I and III) playing crucial roles in oxidative phosphorylation. The cleaved DJ-1 protein, which has 26-fold higher proteolytic activity than the full-length form (Chen et al. 2010), ensures complex I and III efficiency and mitochondrial performance (e.g. apoptosis, ATP production, and lipid and amino acid production and recycling) during the recovery from I/R injury. These studies suggest the potential of active DJ-1 delivery to the heart in managing the after-effects of ischemic injury.
Cerebral I/R injury

Ischemic stroke is a severe neurological health threat worldwide, characterized by brain tissue necrosis leading to acute loss of cerebral blood flow, neuronal dysfunction, and death (Moretti et al. 2015). The cerebral neuroinflammatory cascade is triggered by the endogenous necrotic brain tissue damage-associated molecular patterns (DAMPs) in the plasma promotes I/R injury (Dayon et al. 2011). Rapid accumulation of ROS followed by ischemic damage and renowned neuroprotective functions of DJ-1 in managing ROS led researchers to discover obvious links between DJ-1 and I/R injury.

Neuroprotective impacts of intracellular DJ-1 antioxidant activity against ischemia-induced brain injury in endothelin-1 injection mice (Aleyasin et al. 2007) and intraluminal-introduced middle cerebral artery occlusion reperfusion (MCAO/R) rats (Yanagisawa et al. 2008) have been reported. Similarly, DJ-1 enhanced the neuroprotective function of astrocytes by Nrf2/ARE pathway-mediated GSH upregulation in vitro under oxygen and glucose deprivation/reoxygenation (OGD/R) conditions mimicking I/R insult (Peng et al. 2019). Using the OGD/R primary astrocytes and MCAO/R rats, another recent study demonstrated that DJ-1 suppressed astrocyte neuroinflammatory regulators, including TNF-α, IL-1β, and IL-6 during cerebral I/R injury (Peng et al. 2020). This study discovered a new DJ-1 role in anti-inflammation that facilitates the association between Src-homology 2-domain containing protein tyrosine phosphatase (SHP)-1 and TNF receptor-associated factor 6 (TRAF6). This SHP-1-TRAF6 interaction negatively regulates TRAF6’s association with NOD-like family member 1, which is critical in regulating inflammation during cerebral I/R injury. Furthermore, hypoxic-ischemic-induced DJ-1 translocation into the healthy mitochondria and further extracellular secretion ensure endogenous neuroprotection in primary rat neural cells (Kaneko et al. 2014). A recent study reported that overexpression of DJ-1 can alleviate pathological brain injury and regulate inflammatory cytokines during I/R injury (Zhao et al. 2021). In an MCAO/R mouse model, adeno-associated viruses-induced DJ-1 upregulation improved neurological function by increasing the anti-inflammatory cytokines IL-10 and IL-4 expression and reducing the pro-inflammatory cytokines IL-1β and TNF-α levels. Thereby, DJ-1 emerges as a prospective drug target for managing cerebral I/R injury.

However, another recent study by Nakamura et al. reported that the extracellular release of DJ-1 from necrotic brain cells stimulates infiltrating macrophages activating a post-ischemic inflammation cascade in an MCAO/R mouse model (Nakamura et al. 2021). They discovered a novel role of extracellular DJ-1 as a DAMP which is distinct in the context of intracellular DJ-1 functions. Due to rapid oxidation in the extracellular space, cysteine residues in secreted DJ-1 become inactivated; thereby, DJ-1 loses its antioxidant capacity. Instead, DJ-1 acts as a PRX-like peroxidase in the plasma to activate the toll-like receptor (TLR2- and TLR4)-mediated inflammatory cytokine production in myeloid cells in ischemic stroke. Targeting DAMPs has been considered promising for cerebral pathologies, so extracellular DJ-1 might be an excellent therapeutic candidate for attenuating cerebral inflammation and tissue injury.

Immuno-inflammation

DJ-1’s activity in mediating ROS-induced inflammation, particularly in generously expressed neurons and glial cells in the CNS, has been emerging. Downregulation of DJ-1 promotes glial neuroinflammation and dopaminergic neuron loss in the MPTP-induced PD mice model (Stock & Schwab 2006) and accelerates neointima formation by upregulating Na+/H+ exchanger 1 (NHE1)-mediated inflammatory cell migration (Zhang L et al. 2020). In MS pathophysiology, DJ-1 might confer astrocyte-mediated neuroprotection since consistent overexpression of DJ-1 and Nrf2 has been reported in MS injuries (Hirotani et al. 2008, van Horssen et al. 2010). DJ-1 negatively regulates NLRP3 inflammasome activation via upregulated Nrf2/TNF receptor-associated factor 6 (TRAF6). This SHP-1-TRAF6 interaction negatively regulates TRAF6’s association with NOD-like family member 1, which is critical in regulating inflammation during cerebral I/R injury. Furthermore, hypoxic-ischemic-induced DJ-1 translocation into the healthy mitochondria and further extracellular secretion ensure endogenous neuroprotection in primary rat neural cells (Kaneko et al. 2014). A recent study reported that overexpression of DJ-1 can alleviate pathological brain injury and regulate inflammatory cytokines during I/R injury (Zhao et al. 2021). In an MCAO/R mouse model, adeno-associated viruses-induced DJ-1 upregulation improved neurological function by increasing the anti-inflammatory cytokines IL-10 and IL-4 expression and reducing the pro-inflammatory cytokines IL-1β and TNF-α levels. Thereby, DJ-1 emerges as a prospective drug target for managing cerebral I/R injury.

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characterized by the ROS-mediated mast cell activation followed by bioactive inflammatory cytokines release neutralizing aggregated antigens (Kim DK et al. 2013). DJ-1 deficiency encourages high ROS levels in allergic patients with AD and enhances passive cutaneous anaphylaxis outcomes and mast cell degranulation in mice (Kim DK et al. 2013). In addition, DJ-1 as a scaffolding protein promotes interaction between STAT1 and SHP-1 to repress STAT1 activation in astroglia cells. Thus, as a negative regulator of STAT1, DJ-1 controls neuroinflammation that lessens with loss of DJ-1 functions, as seen in PD patients (Kim J et al. 2013). To summarize, DJ-1 negatively affects ROS production and inflammation to modulate host innate and adaptive immune responses; these DJ-1 attributes can be employed to propose new therapeutic candidates for immune-inflammation management.

**Concluding remarks**

The importance of redox regulation in pathogenesis is well recognized. DJ-1 as a redox sensor preferentially undergoes oxidation of cysteine residue at position 106 (C106) under oxidative stress. The oxidation of C106 to the sulfinate (Cys-SO$_2$H) is required for DJ-1 to sense ROS signaling and facilitate cytoprotective pathways crucial for cellular homeostasis. However, further oxidation to sulfonate (Cys-SO$_3$H) significantly affects DJ-1’s structure and functions and correlates with aging and neurodegeneration. DJ-1-deficient mice are viable and fertile, although comparatively more sensitive to oxidative insults (Kim et al. 2005), implying that DJ-1 dysfunction is associated with distinct pathophysiological conditions. Therefore, the upregulation of DJ-1 activity or inhibition of DJ-1 over-oxidation might be therapeutically beneficial. In addition, since DJ-1 senses both intracellular and extracellular redox states and its extracellular secretion is associated with severe pathophysiological conditions, it is essential to analyze its secretion mechanism. It also demands further consideration that although increased DJ-1 confers cytoprotection against apoptosis-induced premature cell death in PD, overexpression of DJ-1 promotes uncontrolled cell transformation in carcinoma. Despite the progressive achievement in DJ-1 research, especially in the last decade, several complicated and, in some instances, contradictory DJ-1 properties under distinct experimental conditions have been reported. Thus, further studies of the roles of DJ-1 in cellular redox response might pave the way for innovative and critical tools of pathogenesis and therapeutic targets of oxidative stress-related diseases.


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