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Neuroprotective role and mechanistic insights of DJ-1 dimerization in Parkinson's disease

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Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disorder primarily driven by the degeneration of dopaminergic neurons, with limited therapeutic interventions currently available. Among the critical factors in PD pathogenesis, DJ-1, a multifunctional protein, has emerged as a key neuroprotective agent against oxidative stress—a major contributor to the disease. Recent research has emphasized the pivotal role of DJ-1 dimerization in enhancing its neuroprotective capabilities. This review provides an in-depth analysis of the molecular mechanisms underlying DJ-1 dimerization and its relevance to PD. Specifically, we specifically explore how dimerization stabilizes DJ-1, enhances its antioxidative properties, improves mitochondrial function, and modulates key cellular pathways essential for neuronal survival. Furthermore, we discuss the molecular determinants governing DJ-1 dimerization, highlighting its potential both as a biomarker for PD diagnosis and a promising therapeutic target. By synthesizing current advancements, we propose that targeting DJ-1 dimerization may offer innovative strategies to slow PD progression and bolster neuronal health. This review positions DJ-1 as a central focus in PD research, paving the way for future studies aimed at developing neuroprotective therapies.

Keywords Parkinson's disease, DJ-1, Dimerization, Mitochondrial function, Neuroprotection

Graphical Abstract

Neuroprotective Role of DJ-1 Dimers and Their Regulation in PD. This schematic highlights the neuroprotective role of DJ-1 dimers in PD. Post-translational modifications (PTMs) such as oxidation (O), phosphorylation (P), and S-nitrosylation (S), as well as molecular chaperones like BAG1, regulate the formation of DJ-1 dimers. DJ-1 dimerization is emphasized as a critical feature for stabilizing its structure and enhancing its neuroprotective functions, including antioxidative stress regulation (mitigating reactive oxygen species [ROS]), mitochondrial homeostasis, molecular

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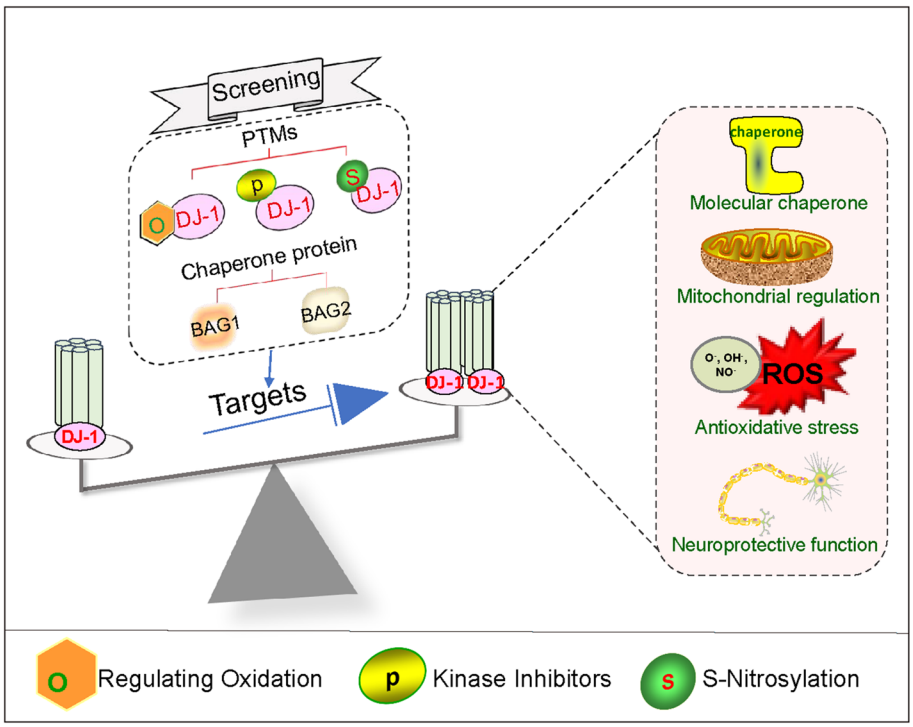
chaperone activity, and neuronal survival. Therefore, screening for factors that regulate DJ-1 dimer formation may represent a novel therapeutic target for protecting neurons.



Background

Parkinson's disease (PD) is a progressive neurodegenerative disorder primarily characterized by motor symptoms and the presence of Lewy bodies in the brain [1]. Its pathogenesis involves complex mechanisms, including oxidative stress, mitochondrial dysfunction, and impaired protein degradation [1, 2]. While the exact causes of PD remain elusive, genetic studies have identified mutations in key genes, such as *SNCA, LRRK2, PARKIN, PINK1*, and *DJ-1*, which provide significant insights into the disease's underlying mechanisms [3, 4]. Among these, DJ-1 (encoded by PARK7) has emerged as a critical player due to its neuroprotective role in counteracting oxidative stress and maintaining mitochondrial integrity—both pivotal factors in PD pathogenesis [5–7].

DJ-1, located on chromosome 1 (1p36.12–1p36.33), was initially identified as an oncogene product in 1997 [8]. Its importance in neuroprotection became evident later when mutations in PARK7 were linked to autosomal recessive early-onset PD [9]. As a highly conserved member of the ThiJ/Pfpi superfamily [10], DJ-1 is ubiquitously expressed across tissues, including the brain, and localizes to the cytoplasm, nucleus, and mitochondria [11]. Its diverse cellular roles include protection against oxidative damage, transcriptional regulation, and exhibiting protease and chaperone-like activities [5, 12, 13].

Under physiological conditions, DJ-1 primarily exists as a homodimer, a flexible and reversible structure that enables its interaction with various partner proteins to perform diverse cellular functions [14–16]. The dimerization process relies on specific amino acid residues, which stabilize the protein and enable it to perform its neuroprotective functions [17]. Disruptions in dimerization compromise DJ-1's stability, increase vulnerability to oxidative stress, and promote protein aggregation—a hallmark of neurodegenerative disorders [18]. Furthermore, in sporadic PD cases, detergent-insoluble DJ-1 dimers are often found at elevated levels, underscoring the potential link between dimerization anomalies and PD pathology [19–21].

Understanding the structural and functional dynamics of DJ-1 dimerization holds great promise for elucidating PD mechanisms and developing targeted therapies. Stabilizing DJ-1 dimerization, either through small molecules or gene therapy, has the potential to enhance neuronal resilience against oxidative stress, offering innovative approaches

for treating both familial and sporadic forms of PD. By focusing on these mechanisms, we can pave the way for interventions aimed at slowing disease progression and improving patient outcomes. This study seeks to advance our understanding of DJ-1 dimerization and its therapeutic potential, thereby contributing valuable insights to the broader field of neurodegenerative disease research.

DJ-1 structure

DJ-1, also known as PARK7, is a small, highly conserved protein consisting of 189 amino acids with a molecular weight of approximately 20 kDa [22]. It belongs to the ThiJ/Pfpl superfamily, characterized by a conserved cysteine residue crucial for its enzymatic and protective functions [23]. DJ-1 is involved in various cellular processes, including antioxidative stress response, chaperone activity, and cellular signaling, particularly in the context of neurodegenerative diseases such as PD [24]. The primary structure of DJ-1 highlights its functional features, with a relatively unstructured N-terminal region that provides flexibility for interacting with diverse partners and a C-terminal region containing the catalytic triad-like motif, including Cys106, His126 and Glu18, critical for DJ-1's antioxidative and protective roles [25]. Under stress conditions, Cys106 undergoes oxidative modifications, enabling different functional states of the protein [23]. Structurally, DJ-1 predominantly comprises β-sheets and α-helices organized into a compact globular form, stabilized by intramolecular hydrogen bonds and hydrophobic interactions that ensure stability and functionality [17, 25–27]. The C-terminal domain, more complex and functionally significant, forms the protein's core with a central β-sheet surrounded by α-helices and loops. Its C-terminal contains an additional α-helix (H-helix), which is unique to the DJ-1 protein and closely associated with its dimerization pattern [25]. These structural and functional characteristics underscore the importance of DJ-1 in maintaining cellular homeostasis and its relevance to neurodegenerative disease mechanisms.

The crystal structure of DJ-1 reveals that it adopts a "helix-strand-helix" sandwich configuration and primarily exists as a dimer. The dimer interface is formed through interactions involving α-helices (αA, αG, and αH) and β-strands (β3 and β4). This interface is stabilized by eight pairs of hydrogen bonds and numerous van der Waals interactions, ensuring the dimer's structural stability [26, 28]. Notably, the residues at the dimer interface are highly conserved among DJ-1 family proteins, indicating that this dimeric form is both stable and functionally significant [25]. The active site of DJ-1, which is located near the dimer interface, contains conserved residues such as Cys-106 and His-126 [25]. This spatial arrangement suggests that the dimeric structure is critical for DJ-1's enzymatic and protective functions, although this hypothesis remains unproven [29]. DJ-1 predominantly exists as a homodimer in its functional state, with dimerization being essential for its biological activities [30, 31]. Structural studies have identified specific regions and residues that contribute to the formation and stabilization of the dimer. These findings highlight the functional importance of DJ-1 dimerization and provide insights into its role in maintaining cellular homeostasis, which is particularly important in neurodegenerative diseases such as PD.

Regulatory mechanisms of DJ-1 dimerization

The dimerization of DJ-1 is crucial for its structural integrity and protective functions in cellular processes, including antioxidative stress responses and neuroprotection in PD. This process is regulated by various structural elements, specific interactions, and external factors such as mutations and oxidation states. In this section, we will examine the key factors that regulate DJ-1 dimerization, including the role of the C-terminal helix-kink-helix motif, oxidation, and mutations, as well as how environmental factors contribute to its dimerization state (Fig. 1).

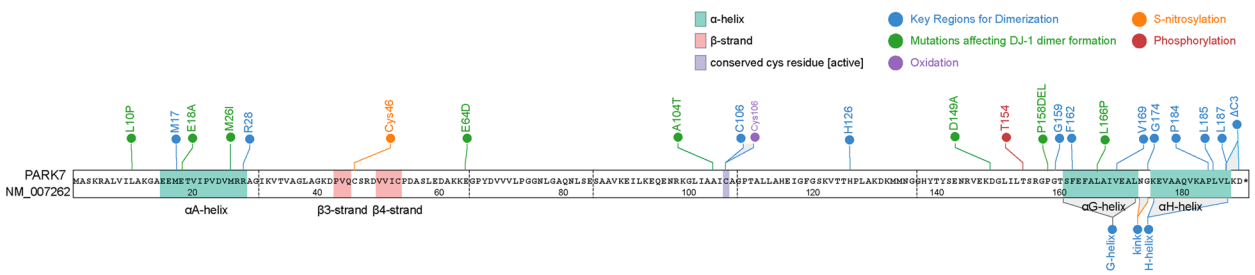


Fig. 1 The Impact of Key Structural Features and Mutations on DJ-1 Dimerization. The schematic highlights the critical structural determinants that influence DJ-1 dimer formation, including the identified pathogenic mutations that disrupt dimer stability. Additionally, it illustrates the post-translational modification sites implicated in the regulation of DJ-1 dimerization

The role of the C-terminal helix-kink-helix motif and key determinants in DJ-1 dimerization

The DJ-1 protein features a distinctive C-terminal fold composed of two α-helices (designated as G and H) connected by a kink [32]. These helices are highly conserved, with glycine at position 174 enabling the formation of tight structural turns. Experimental evidence suggests that this unique C-terminal helix-kink-helix motif not only differentiates DJ-1 from other proteins in its superfamily but also plays a pivotal role in maintaining its structural integrity and functional activity. While the H-helix contributes minimally, Experimental evidence suggests that this unique C-terminal helix-kink-helix motif not only differentiates DJ-1 from other proteins in its superfamily but also plays a pivotal role in maintaining its structural integrity and functional activity [32].

Given the structural characteristics described above, DJ-1 dimerization is primarily mediated by hydrophobic interactions at the dimer interface. A hydrophobic patch, formed by residues located in the αG and αH helices, plays a critical role by excluding water molecules, thereby stabilizing the dimer structure [26, 27]. This patch also facilitates interactions with unfolded substrate proteins, enhancing DJ-1's chaperone function [28]. Additionally, specific interactions, such as hydrogen bonds (e.g., between His-126 and Pro-184) and hydrophobic contacts involving residues like Met-17 and Phe-162, further reinforce the stability of the dimer interface [33]. Notably, the αH-helix's interaction with the αA and αG helices contributes to the formation of a hydrophobic core, which is crucial for the dimer's overall structural stability [25] (Fig. 1).

Mutational studies provide additional insights into the mechanisms of dimerization. For instance, computational modeling of the R28A mutation reveals that this mutation significantly weakens subunit interactions within the dimer without altering the monomeric structure of DJ-1. This disruption is attributed to the loss of key salt bridges and hydrophobic interactions at the dimer interface, resulting in a marked reduction in dimer stability [34]. the last three amino acids of the C-terminus (DJ-1 ΔC3) and the hydrophobic residue L187 are indispensable for dimer formation and biological functions such as homodimerization, deglycation activity, and suppression of ferroptosis [27]. In summary, these findings underscore the importance of the unique C-terminal helix-kink-helix motif and specific hydrophobic interactions at the dimer interface in maintaining DJ-1's structural stability and functional versatility. Mutations disrupting these structural elements or key residues significantly impair dimerization and related biological functions, highlighting their critical role in DJ-1's involvement in cellular processes (Fig. 1).

The dimerization of DJ-1 is also influenced by the oxidation state of Cys106. Under oxidative stress, Cys106 can be oxidized to cysteine-sulfinic acid, a modification that can induce conformational changes conducive to dimerization. Through dynamic regulation of oxidation states, this modification protects the protein by reducing irreversible oxidative damage. The oxidation of C106 to sulfinic acid (C106-SO2H) has been found to enhance the dimer's protective function under oxidative stress conditions [24]. However, further oxidation to sulfonic acid (C106-SO3H) can disrupt dimer formation, leading to the monomerization of DJ-1 and a loss of its protective functions [35]. This transition highlights a balance in which controlled oxidative modification of C106 supports protective functions, while excessive oxidation disrupts dimerization and undermines structural stability. This oxidative modification is thought to protect the protein from irreversible oxidative damage and is linked to the protective functions of DJ-1 in the cell [14]. These findings suggest that the oxidation of C106 is tightly regulated to maintain DJ-1's structural and functional integrity. Mutations at these residues, particularly those associated with familial PD, can impair dimerization, further emphasizing their functional significance (Fig. 1).

The impact of mutations on DJ-1 dimer formation

The L166P mutation associated with PD profoundly impacts the structural integrity of the DJ-1 dimer, which is critical for its protective cellular function. Disruption of the dimer interface, as seen with the L166P mutation, is strongly linked to familial forms of PD [9], highlighting the necessity of proper dimerization for maintaining DJ-1 functionality. This mutation prevents normal dimer formation, instead promoting the assembly of high molecular weight (HMW) oligomers. As a result, DJ-1 becomes unstable, misfolds into a monomeric state, and undergoes rapid degradation, leading to significant functional impairment [36, 37].

Mechanistically, the L166P mutation destabilizes the dimer interface by disrupting key structural elements, particularly the G-helix and essential intermolecular contacts. This disruption increases the hydrophobic surface area, enhances the propensity for aggregation, and induces a variety of distorted conformations. These structural changes collectively impair DJ-1 dimerization and its proposed chaperone function, further destabilizing the protein [33, 38]. Additionally, the mutation destabilizes the C-terminal αG helix and the hydrophobic core, exacerbating the overall instability of the DJ-1 protein [25]. The mutation further induces structural disorder around Cys-106, a residue critical for DJ-1's stability and function, by disrupting its hydrogen bond with Glu-18. This loss of structural integrity around Cys-106 further

compromises the dimer interface, highlighting the deleterious effects of L166P on DJ-1 functionality [33].

Several other mutations, including D149A, P158DEL, L10P, A104T, E18A, and E64D, also interfere with DJ-1 dimer formation [22, 26]. These mutations can be broadly categorized into three groups: mutations that completely inhibit dimer formation (e.g., L166P, L10P), mutations that impair homodimerization but allow heterodimerization with wild-type DJ-1 (e.g., D149A, P158DEL, E18A), and mutations that weaken dimer stability under stress (e.g., E64D). D149A, E18A, and P158DEL mutations disrupt DJ-1's self-associative interactions but still form functionally inactive heterodimers with wild-type DJ-1 [29, 39, 40]. However, the heterodimers are functionally inactive, meaning that the presence of the D149A mutant can exert a dominant-negative effect on the wild-type protein [22]. For example, the E18A mutation, which disrupts the catalytic triad of DJ-1 (E18, H126, C106), compromises homodimer formation by destabilizing key dimer interactions [40]. Similarly, the deletion of P158 affects the G-helix, a crucial structural element for dimerization [29]. And Proline-158 is located in a critical β-turn near the dimer interface and is essential for dimer stability [39].

The L10P mutation precludes both self-dimerization and heterodimerization with wild-type DJ-1, indicating a complete loss of dimerization capability [41]. Interestingly, conflicting findings have been reported regarding L10P's ability to form heterodimers with wild-type DJ-1. One study suggested that L10P retains heterodimerization ability [29], while others reported the opposite. These discrepancies might arise from differences in experimental conditions, such as buffer composition, detection sensitivity, or cell line models. Further studies standardizing experimental variables are needed to resolve these contradictions. The L10P is located in the β-strand structural region, which does not directly affect the dimer interface but indirectly hinders dimerization by altering protein folding [29]. Misfolded L10P protein cannot self-associate into homodimers, indicating that structural integrity is a prerequisite for proper dimerization.

The A104T mutation alters the conformation of the α6 region, disrupting dimerization while leaving the α7 and α8 regions largely unaffected [42]. Both the L166P and A104T mutations significantly increase the free energy required for DJ-1 dimerization, reducing its probability [42]. And, in wild-type DJ-1, the dimer interface is stabilized by critical interactions, including hydrogen and ionic bonds such as His126 – Pro184', Glu18 – Arg28', and Gly159 – Leu185'. These stabilizing interactions are disrupted in the L166P and A104T mutants, further impairing dimerization. The A104T mutant, located in β-strand 7, causes local structural changes that propagate to surrounding regions, particularly near Cys-106, a residue critical for DJ-1's antioxidant function [18]. In contrast, the M26I mutation uniquely preserves these key interactions, maintaining a relatively stable dimer interface [42]. The M26I mutation, located at the subunit interface, minimally affects dimerization due to structural and volumetric similarities between methionine and isoleucine [43]. Both computational analyses and experimental results suggest that the M26I mutant forms dimers comparable to the wild-type, without major alterations to the dimeric structure [34]. However, while M26I preserves key dimer interactions, it compromises the stability of the α1-helix, increasing aggregation risk and weakening dimer-forming activity compared to wild-type DJ-1 [40].

The E64D mutant retains the capacity to form homodimers but exhibits reduced stability under oxidative stress. This mutation alters DJ-1's hydrodynamic and electrostatic properties, increasing aggregation propensity, which may contribute to PD pathogenesis [41]. In summary, mutations affecting DJ-1 dimerization can disrupt its stability, self-associative interactions, or stress resistance, collectively impairing its protective role in cells (Table 1 and Fig. 1).

The impact of environmental factors on DJ-1 dimer formation

In addition to the structural changes of DJ-1 itself, environmental factors can also cause the dimerization state of DJ-1 and even lead to the formation of abnormal dimers. High concentrations of retinoid N-(4-hydroxyphenyl) retinamide (4-HPR, 10 μM) reduce the formation of DJ-1 dimers, as shown by DSS cross-linking analysis [44]. Studies have shown that environmental factors, such as paraquat and diquat, which generate free radicals (such as superoxide, $O_2^{\bullet -}$ and hydroxyl radicals, $^{\bullet}OH$) directly affect DJ-1 by inducing the formation of SDS-resistant DJ-1 dimers (resistant to sodium dodecyl sulfate (SDS), meaning they are not easily separated in routine biochemical analyses.). Unlike the functional SDS-sensitive dimers (sensitive to SDS, meaning they can be easily separated in routine biochemical analyses) typically associated with DJ-1 activity, these SDS-resistant dimers are irreversible and dysfunctional [15]. The formation of such dimers compromises the antioxidative function and deprive the chaperone function of DJ-1, making dopaminergic cells more susceptible to oxidative stress and potentially contributing to the development of PD [15]. Moreover, sporadic PD cases often exhibit increased levels of detergent-insoluble DJ-1 dimers, further implicating dimerization anomalies in disease pathology [19–21]. And many pathological mutants of DJ-1 (E64D, R98Q, A104T, D149A and E163K) form SDS-resistant dimers

Table 1 Structural and functional impacts of DJ-1 mutations on dimerization

Mutation	Location	Effect on Dimerization	Structural Changes	Functional Consequences	Ref
L166P	C-terminal	Completely inhibit dimer formation	Disrupts C-terminal αG helix and hydrophobic core; destabilizes interactions between αG and αH; Abolishes critical inter-monomer bonds (His126–Pro184′, Glu18–Arg28′, Gly159–Leu185′); Introduces large structural deviations in αF, αG, and αH regions, exposing hydrophobic surfaces; breaks Cys-106 hydrogen bond; increase in the free energy of dimerization	Destabilizes protein, increases misfolding and aggregation, impairs protective role	[25, 33, 36–38]
A104T	β−7strand	Prevents dimer formation	Alters the α-F helix region, reorienting the Cys106 loop; Disrupts critical interactions (His126 − Pro184′, Glu18 − Arg28′, and Gly159 − Leu185′) increase in the free energy of dimerization	Impairs antioxidative function	[42]
P158Δ	Near the start of the αG-helix	Drastically reduces heterodimers with wild-type DJ-1, no homodimers	Disrupts α- G helix and β-turn	Fails to protect cells from oxidative stress and apoptosis; Misfolding-driven aggregation	[29, 39]
L10P	β−1-strand	Completely inhibit dimer formation	Located in the first β-strand, though not directly in the dimerization interface, it disturbs the local folding	High aggregation, toxic under stress	[29, 41]
D149A	β−10 strand	Forms heterodimers with wild-type DJ-1, no homodimers	disrupts key intermolecular interactions that stabilize the dimer interface; reduced structural integrity of the dimer	Decreased dimer stability, impaired antioxidative function; Reduces dimerization efficiency	[22, 29, 40]
E18A	Near α- A helix	Forms heterodimers with wild-type DJ-1, no homodimers	part of the catalytic triad of DJ-1 (E18, H126, C106) and serves as a critical site for dimer formation	Alters its subcellular localization, and predominantly transported to the mitochondria instead of being distributed in the cytoplasm,	[40]
E64D	α- C helix	Retains dimerization ability	Alters hydrodynamic and electrostatic properties; Minimal perturbations near mutation site	Promotes protein aggregation; may alter protein–protein interactions	[41]
M26I	β−10 strand; Near the dimer interface	Retains dimerization ability; Reduced dimer stability	No significant change in free energy; Methionine and isoleucine have comparable hydrophobic properties, minimizing structural disruptions; Disruption of α-helix 1 and weakened dimer interface	Increased monomeric form, reduced antioxidative defense; Increases aggregation tendency	[34, 40, 42, 43]

[15]. So, abnormal DJ-1 dimers may influence the development of familial and sporadic PD.

The essential role of DJ-1 dimerization in protecting against PD pathogenesis

DJ-1 plays a critical role in protecting cells against oxidative stress, with its dimerization essential for its neuroprotective functions (Fig. 2). Mutations that impair dimer formation disrupt DJ-1's stability, localization, and activity, contributing to PD progression. This section explores the impact of such mutations on the stability and function of DJ-1 dimers, their subcellular localization, and their role in safeguarding neurons from oxidative damage. We will also discuss how these disruptions are linked to the pathogenesis of PD.

Comparison of stability and activity between dimeric and monomeric forms of DJ-1

DJ-1 mutations such as M26I, A104T, L10P, P158DEL and D149A weaken the interactions at the dimer interface, making the protein more prone to degradation and aggregation [18, 29]. Experimental data show that the

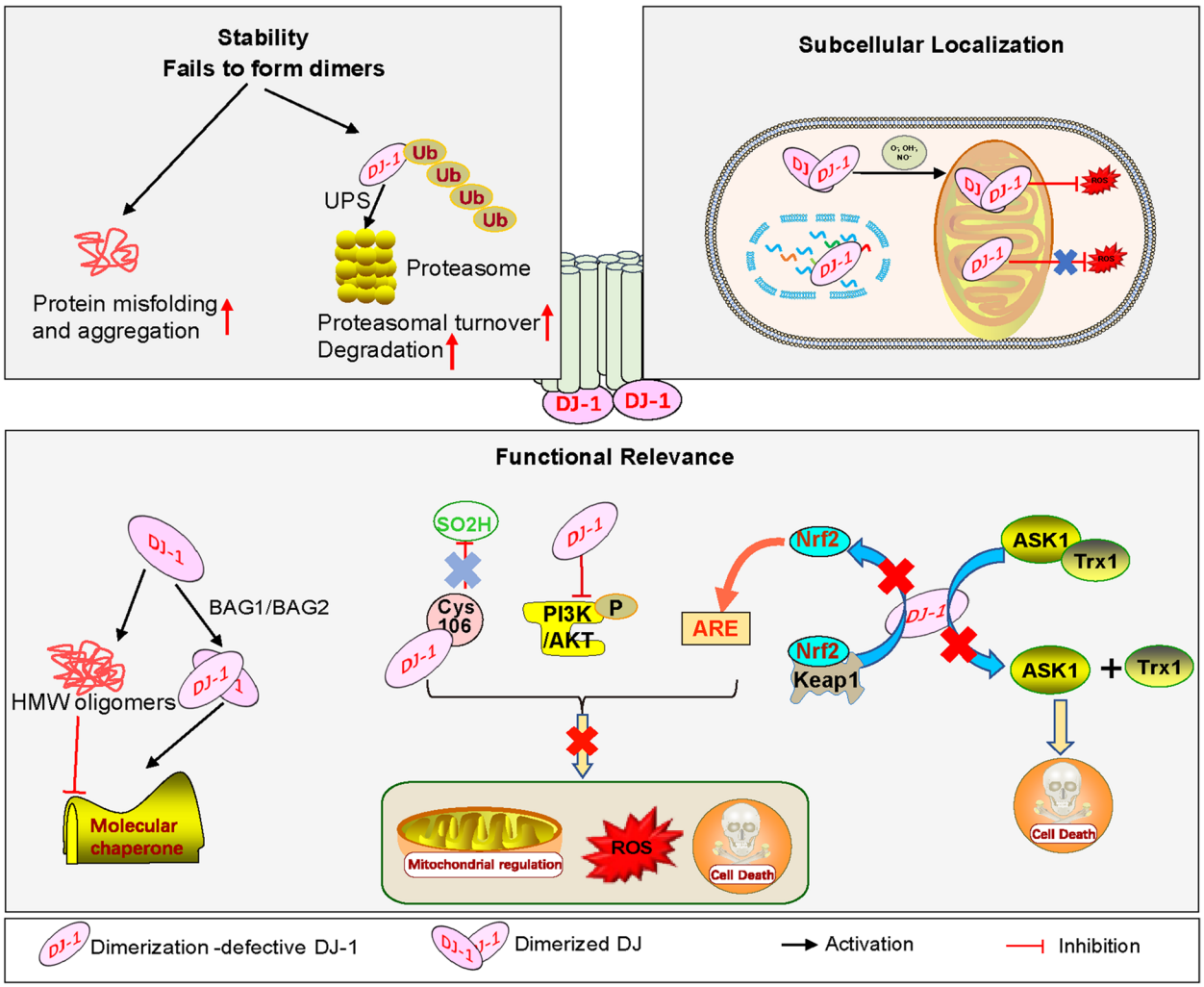


Fig. 2 Impacts of DJ-1 Dimerization on its Structural Stability, Functional Roles, and Subcellular Localization. This figure illustrates the multifaceted consequences of disrupted DJ-1 dimerization in the context of Parkinson's disease (PD). The loss of DJ-1 dimer leads to increased proteasomal degradation, diminished antioxidative stress capacity, and impaired mitochondrial function. Abnormal subcellular localization and the accumulation of misfolded DJ-1 mutants further exacerbate oxidative stress and protein aggregation, which are key contributors to neuronal toxicity. Additionally, disrupted dimerization compromises DJ-1's molecular chaperone activity and its interaction with key cellular signaling pathways, such as PI3K/ Akt, Nrf2/ ARE, and the ASK1 pathway, ultimately promoting the degeneration and death of dopaminergic neurons. ASK1 apoptosis signal-regulating kinase 1; ARE antioxidant response element; Akt protein kinase B (PKB, also known as AKT); Nrf2 nuclear factor erythroid 2-related factor; HMW high molecular weight; PI3K phosphatidylinositol 3-kinase; ROS reactive oxygen species; Trx1 thioredoxin 1; Ub Ubiquitin; UPS ubiquitin–proteasome system

L166P and V169P mutants exhibit a half-life reduction, coupled with a threefold increase in proteasomal turnover rates. This instability contrasts with the wild-type and M26I mutant, both of which maintain their dimeric state and stability [32, 43]. The instability of this mutant has been implicated in the development of PD because the normal DJ-1 protein exists as a dimer and helps to protect cells from oxidative stress damage [25]. The L166P mutant undergoes selective polyubiquitination and is degraded through the 26S proteasome, suggesting that misfolding caused by the mutation exposes degradation signals. This is relevant to the pathological process of PD, as protein misfolding and aggregation are key factors in neuronal damage in PD [45]. For example, ubiquitin-binding studies reveal increased ubiquitination levels for L166P mutants compared to wild-type DJ-1. However, wild-type DJ-1 does not exhibit similar ubiquitination, indicating that the mutation directly leads to an abnormal degradation pathway [37]. The DJ-1 T154A mutant, which cannot be phosphorylated at Thr154, fails to form homodimers. The T154A mutant Phosphorylation-deficient T154A mutants is prone to degradation via the ubiquitin–proteasome system, highlighting that dimerization is crucial for protecting DJ-1 from cellular degradation pathways [46] (Fig. 2).

Impact of disrupted dimer formation on subcellular localization of DJ-1

The formation of homodimers is closely associated with subcellular distribution. Wild-type DJ-1 is predominantly localized in the cytosol and mitochondria, whereas, due to impaired folding, the L166P mutant cannot form functional dimers and exhibits abnormal localization in the nucleus and mitochondria within cells [16, 47]. Interestingly, while mutations such as E18A and L166P impair dimer formation, these mutants still localize to mitochondria, suggesting that the monomeric form of DJ-1 may preferentially localize to mitochondria and this abnormal localization is potentially linked to PD pathological processes [40]. Mutations at critical dimer interface residues, such as C46S and C53A, show similar mitochondrial localization patterns [40]. Studies have shown that DJ-1 can translocate from the cytoplasm to the mitochondria upon oxidative stress induction, and this translocation process is closely associated with dimer formation [31]. This suggests that DJ-1's mitochondrial transport is dimerization-independent, though functional roles within mitochondria may differ between monomeric and dimeric forms [40]. And dimer formation in mitochondria is posited to be critical for DJ-1's protective roles, with monomeric forms contributing to mitochondrial dysfunction [40]. For instance, dimeric DJ-1 translocate to mitochondria under oxidative stress, playing a role in maintaining mitochondrial integrity and promoting mitophagy (clearance of damaged mitochondria) [5]. And oxidative stress and mitochondrial dysfunction are closely related to PD [2]. Based on these findings, the presence of DJ-1 as a dimer in mitochondria is essential for its role against oxidative stress and thus for its neuroprotective role in PD (Fig. 2).

Impact of disrupted dimer formation on the functional roles of DJ-1

The L166P mutation disrupts DJ-1's intrinsic folding propensity, weakening its ability to interact with itself or other molecules [37]. The high molecular weight aggregates caused by the L166P mutation may induce additional toxic effects, exacerbating PD pathology through the accumulation of misfolded proteins and abnormal protein–protein interactions [34]. The homodimerization of DJ-1 is essential for its role as a molecular chaperone and foldase, essential in mitigating the toxic protein aggregation often observed in PD. Loss of dimerization capacity directly leads to functional loss. Studies using DJ-1 mutant models, such as the ΔC3 and L187E mutations, demonstrate that these mutations disrupt DJ-1 homodimerization and result in the loss of its methylglyoxal (MGO) detoxification capacity [27], which has been linked to the onset and progression of PD. BAG1, by stabilizing dimer formation and enhancing molecular chaperone activity, offers a potential therapeutic target for PD [47].

Under oxidative stress conditions—a hallmark of PD pathology—free radicals like superoxide and hydroxyl radicals irreversibly form SDS-resistant dimers of DJ-1, disrupting its dimerization-dependent protective functions [15]. Mutations such as L166P, which prevent homodimerization, are associated with diminished antioxidative activity and exacerbate mitochondrial dysfunction, leading to neuronal toxicity [34, 38, 40]. This is particularly relevant to the progressive degeneration of dopaminergic neurons in PD, where oxidative damage plays a pivotal role [48]. The conserved Cys106 residue, located near the dimer interface, is vital as a sensor of reactive oxygen species (ROS) and directly links DJ-1 to redox regulation in PD. Oxidative modifications at this site influence DJ-1's activity and may impair its ability to counteract oxidative stress, contributing to neuronal vulnerability in PD [14]. Additionally, mutations such as M26I, A104T, and D149A, which impair regions near Cys106, weaken DJ-1's antioxidative stress response, further promoting the neurodegenerative processes characteristic of PD [18].

Mutations in DJ-1, including L166P, M26I, and D149A, as well as alterations in its redox state (e.g., Cys106), especially those affecting its dimerization, severely

disrupt the normal functioning of key cellular signaling pathways, such as phosphatidylinositol 3-kinase (PI3K) / protein kinase B (PKB, also known as Akt), nuclear factor erythroid 2-related factor (Nrf2) / antioxidant response element (ARE), and the apoptosis signal-regulating kinase 1 (ASK1) pathway [12]. The DJ-1 L166P mutation, in particular, leads to a significant reduction in AKT phosphorylation, notably at Thr308 and Ser473, thereby hindering its activation in response to oxidative stress. This impairment ultimately suppresses the AKT signaling pathway and increases the risk of cellular apoptosis [49, 50]. DJ-1 also plays a critical role in stabilizing Nrf2 by promoting its release from the Keap1 complex and facilitating its translocation to the nucleus, where it activates the transcription of antioxidant genes [51]. However, mutations like L166P compromise DJ-1's ability to activate Nrf2 effectively, resulting in reduced Nrf2 activity and loss of the Nrf2/ARE pathway function, which weakens the cell's defense against oxidative damage [52]. Additionally, research has shown that DJ-1 interacts with ASK1 following the dissociation of thioredoxin 1 (Trx1) under oxidative stress. While wild-type DJ-1 can inhibit apoptosis by binding to ASK1, PD-linked mutants, such as L166P, fail to do so, which leads to enhanced apoptosis in dopaminergic neurons [32, 44, 52]. These findings highlight the crucial role of dimeric DJ-1 in cellular survival pathways and its dysfunction in PD pathogenesis.

Furthermore, the severity of damage to DJ-1 dimerization caused by mutations is directly correlated with the extent of its antioxidative and neuroprotective impairments. Severe mutations, such as L166P, profoundly compromise DJ-1's chaperone and antioxidative functions, while moderate mutations (e.g., M26I, A104T, D149A) destabilize dimers, increasing susceptibility to oxidative damage [18]. The active site of DJ-1, which includes conserved residues Cys-106, His-126, and Glu-18, is located near the dimer interface. Disruption of this interface by genetic mutations or environmental factors directly impacts neuronal survival, accelerating PD progression [25]. In summary, these findings emphasize that DJ-1 dysfunction, driven by impaired dimerization, contributes to core aspects of PD pathology, including oxidative stress, mitochondrial dysfunction, protein aggregation, and neuronal death (Fig. 2).

Comparison of DJ-1 dimerization with other PD-related proteins: insights into overlapping and distinct neuroprotective mechanisms

The neuroprotective mechanisms of PD are multifaceted, with multiple proteins contributing to cellular homeostasis, mitochondrial function, and oxidative stress defense. Among these, DJ-1 stands out as a critical player, particularly through its dimerization process, which enhances its antioxidant capacity, protects mitochondrial function, and shields neurons from degeneration. Comparing the dimerization of DJ-1 with other PD-associated proteins, such as Parkin, PINK1, LRRK2, and GBA, provides a broader understanding of both the overlapping and unique neuroprotective mechanisms these proteins employ.

As discussed, DJ-1 dimerizes under oxidative stress and translocate to the mitochondria, where it resides in the mitochondrial matrix, playing a pivotal role in maintaining mitochondrial health [31]. DJ-1 functions as both a sensor for oxidative stress and an antioxidant, providing robust protection against mitochondrial damage [14]. In contrast, Parkin, an E3 ubiquitin ligase, contributes to mitochondrial quality control through mitophagy. PINK1 monitors mitochondrial health by identifying depolarized mitochondria and recruiting Parkin to initiate mitophagy [53]. When mitochondrial function is compromised, the PINK1/Parkin pathway activates autophagy to eliminate damaged mitochondria through signaling mechanisms [54, 55]. Although both DJ-1 and PINK1/Parkin contribute to oxidative stress response and mitochondrial health, DJ-1 dimers primarily focus on enhancing overall antioxidant defense and supporting mitochondrial function, while PINK1/Parkin are more directly involved in mitochondrial surveillance and the clearance of damaged mitochondria. Studies have also indicated that DJ-1 interacts with the PINK1/Parkin pathway to regulate mitophagy [56].

LRRK2, a multifunctional kinase, regulates critical cellular processes, including autophagy, mitophagy, and vesicular trafficking [57]. Mutations in LRRK2 lead to excessive kinase activity, disrupting these processes and contributing to PD pathogenesis [58]. While both DJ-1 and LRRK2 are essential for cellular homeostasis and neuroprotection, their mechanisms differ. DJ-1 dimerizes to regulate redox balance and mitochondrial protection, whereas LRRK2 primarily affects cellular maintenance and degradation pathways, particularly through its kinase activity.

Similarly, both DJ-1 and GBA exhibit neuroprotective effects. DJ-1 dimerization is a dynamic process, enabling it to act directly in both the cytoplasm and mitochondria to resist oxidative damage. In contrast, GBA predominantly influences lysosomal function, which is crucial for cellular homeostasis [59]. Moreover, dimerized DJ-1 acts as a molecular chaperone and foldase [27], playing a significant role in alleviating the toxic protein aggregation commonly observed in PD by reducing the accumulation and toxicity of α-synuclein and Tau proteins.

In summary, the comparison of DJ-1 dimerization with other PD-associated proteins highlights both overlapping and distinct neuroprotective mechanisms. DJ-1,

through its dynamic dimerization, primarily enhances antioxidant defense and supports mitochondrial function, positioning it as a key player in mitigating oxidative stress and maintaining mitochondrial integrity. In contrast, other proteins like Parkin, PINK1, and LRRK2 contribute to mitochondrial surveillance, mitophagy, and cellular maintenance through distinct pathways, such as autophagy and kinase activity. Additionally, DJ-1's unique role as a molecular chaperone adds a layer of protection against toxic protein aggregation, further strengthening its neuroprotective capacity. These comparisons underline the complexity and interconnectedness of neuroprotective pathways in PD, suggesting that targeting DJ-1 dimerization may offer a promising therapeutic strategy.

Regulation of DJ-1 dimerization and its therapeutic implications for PD

The formation of DJ-1 dimers is a complex process influenced by various biochemical conditions and regulated by specific cellular signaling pathways. Understanding the mechanisms that govern DJ-1 dimerization provides critical insights into its neuroprotective functions and its dysfunction in the pathogenesis of PD, offering potential therapeutic targets (Table 2). Figure 3 summarizes these regulatory mechanisms and their implications for DJ-1 dimer stability, highlighting oxidation, S-nitrosylation, phosphorylation, and molecular chaperones as key modulators.

Oxidation and redox regulation of DJ-1

Post-translational modifications (PTMs) such as oxidation play pivotal roles in regulating DJ-1 dimer stability and function. Oxidation is closely linked to the cellular redox environment, which is frequently altered in PD. As shown in Fig. 3, the oxidative state of Cys106—a critical residue for dimer integrity—is tightly linked to cellular redox conditions [25]. In its reduced state (-SH), Cys106 maintains the normal dimer structure and activity of DJ-1. The disulfide bonds between cysteine residues stabilize DJ-1 dimers. Oxidation to the sulfinate form (-SO2H) enhances mitochondrial localization and neuroprotection, whereas over-oxidation to the sulfonate form (-SO3H) destabilizes dimers by exposing more surface area to solvents and reducing intermonomer binding energy and impairs biological activity [23, 25, 35]. Therapeutic strategies targeting the oxidative state of Cys106 to maintain it in its optimal form could preserve DJ-1's neuroprotective function while mitigating damage caused by excessive oxidative stress (Fig. 3, Panel 1). In line with this, antioxidants, as part of the current treatment for PD, have been shown to slow down neurodegenerative changes by reducing oxidative stress. Antioxidants such as vitamins E and C, CoQ10, crocin, fucoxanthin, resveratrol, and various synthetic compounds help reduce oxidative stress, improve mitochondrial function, and protect dopaminergic cells, thus contributing

Table 2 Therapeutic approaches targeting DJ-1and mitochondria for neuroprotection in Parkinson's disease

Protagonist	Mechanisms	Preclinical/clinical status	Functional Consequences	Ref
PKAcα inhibitors	Regulates the formation of DJ-1 dimers	Preclinical stage	Influences protein aggregation, neuronal damage, and mitochondrial function	[46]
Kinetin Triphosphate / USP30	Modulates the PINK1/Parkin pathway	Preclinical stage	Rescues DJ-1 deficiency, improves mitochondrial quality control and autophagy, slows disease progression	[54]
Phenylbutyrate	Regulates gene transcription, increasing expression of antioxidant enzymes, heat shock proteins, enhance DJ-1 expression;	Preclinical studies	Improves neuroprotection by enhancing antioxidant responses and mitochondrial function	[60, 61]
Curcumin	Activates Nrf2 pathway, reduces oxidative stress, Enhances mitochondrial protection	Preclinical studies	Improves mitochondrial function, reduces oxidative stress, protects dopaminergic neurons	[62]
Celastrol	Activates PINK1 and DJ-1 expression; Activates Nrf2 pathway	Preclinical studies	Enhance antioxidant, promote the removal of damaged mitochondria and help restore the health of mitochondria	[63]
Andrographolide	Activated the PINK1/Parkin pathway, Activates Nrf2 pathway	Preclinical studies	Reduced mitochondrial dysfunction, and oxidative stress	[64]
MitoQ	Mitochondrial-targeted antioxidant, inhibits lipid peroxidation, protects mitochondrial function	Clinical trials	Protects mitochondria, reduces oxidative damage, enhances neuroprotection	[65–67]

PKAcα catalytic subunit alpha of protein kinase A, *Nrf2* nuclear factor erythroid 2-related factor

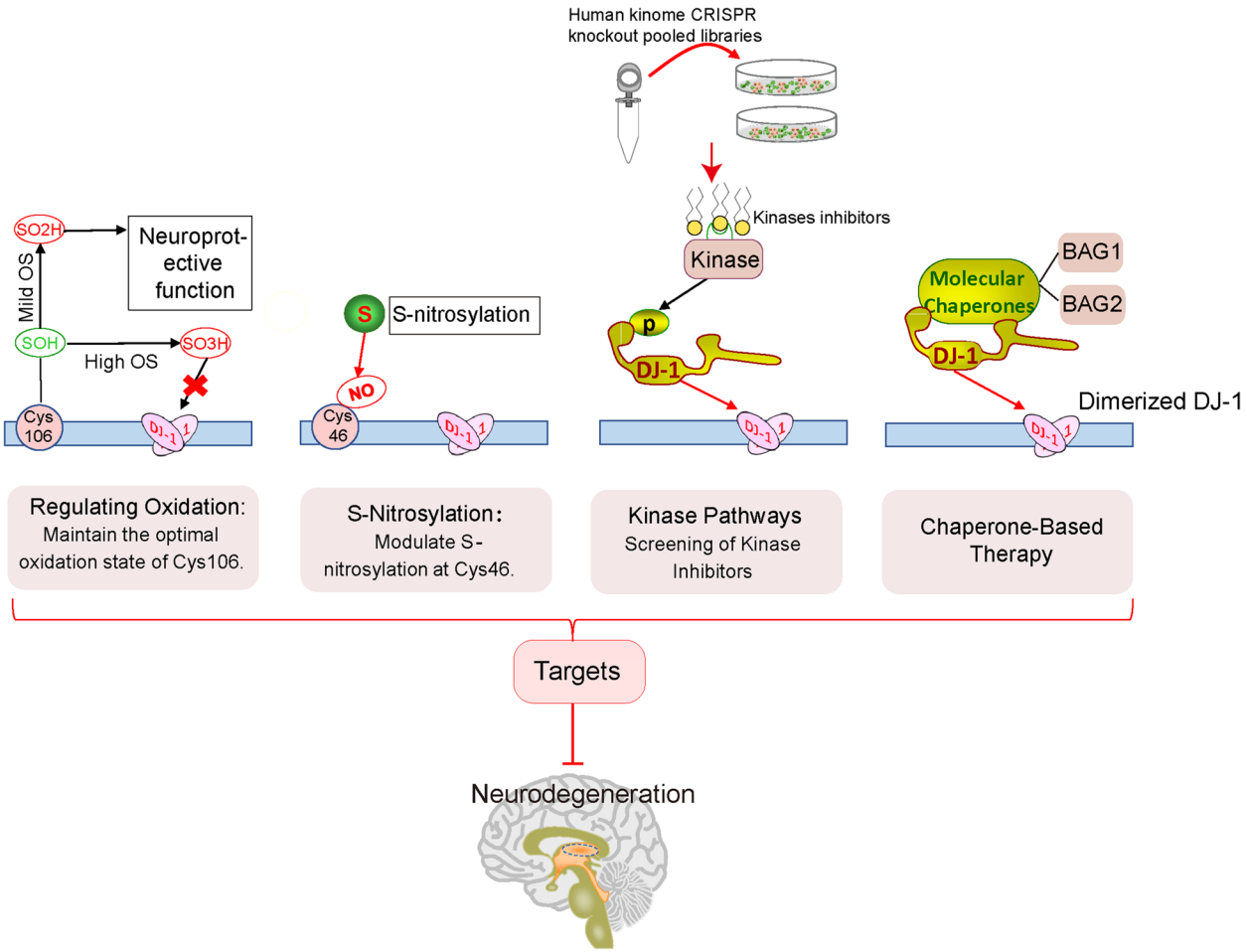


Fig. 3 Regulation of DJ-1 Dimerization and its Therapeutic Implications for Parkinson's Disease (PD). This figure highlights the regulatory mechanisms of DJ-1 dimerization, including key post-translational modifications (oxidation, phosphorylation, S-nitrosylation) and molecular chaperones. Therapeutic strategies targeting these regulatory mechanisms—such as modulating PTMs or enhancing chaperone-mediated dimer stabilization—represent promising avenues for PD treatment. OS Oxidative stress

to the preservation of neuroprotective mechanisms and slowing neurodegeneration in PD [65].

Cys46 and Cys53, other critical cysteine residues, are highly susceptible to S-nitrosylation. Cys46 and Cys106 are evolutionarily highly conserved, suggesting the functional and structural importance of these residues. Cys46 is located close to the dimer interface, as predicted in structural studies [14, 17, 68]. Cys46, located near the dimer interface, is essential for dimerization, as shown by studies where C46S and C46A substitutions severely disrupted dimer stability [40, 68]. As highlighted in Fig. 3, modulating S-nitrosylation at Cys46 could stabilize dimer formation, preventing dimer destabilization under pathological conditions. This represents a promising avenue for therapeutic intervention (Panel 2).

Phosphorylation as a modulator of DJ-1 dimerization

Phosphorylation modifications can play a role in PD through various mechanisms, including influencing protein aggregation, neuronal damage, and mitochondrial function [69, 70]. Additionally, phosphorylation can regulate the structure and function of DJ-1 protein, thereby contributing to the onset and progression of PD [46, 71]. For example, phosphorylation of Thr125 (T125) in DJ-1 enhances enzymatic activity, alters conformation, and affects degradation pathways [71]. Additionally, DJ-1 binds to the catalytic subunit alpha of protein kinase A (PKAcα), resulting in phosphorylation at Thr154 (T154). And phosphorylation at Thr154 by PKAcα impacts DJ-1's subcellular localization and dimer stability, with the T154A mutation significantly reducing dimerization [46]. Given that alterations in DJ-1 function are implicated in

PD, developing PKAcα inhibitors or modulating related kinase pathways might help restore DJ-1 stability and activity, potentially alleviating the neurodegenerative processes seen in PD.

While PKAcα-mediated phosphorylation of DJ-1 at Thr154 is crucial for its dimerization and stability, translating this into clinical practice faces challenges. Developing selective kinase inhibitors must ensure specificity and overcome the blood–brain barrier Additionally, the variability in phosphorylation patterns across different stages of disease and patient profiles complicates the development of universally effective treatments. Nonetheless, targeting DJ-1 phosphorylation, despite limited research on the direct modulation of PKAcα in PD treatment, offers promising therapeutic potential for the disease.

To further advance this, it is essential to explore additional kinases that may regulate DJ-1 dimerization. Based on bimolecular fluorescence complementation (BiFC) technology [72] and the CRISPR knockout kinases library, future research can screen for additional kinases that regulate DJ-1 dimerization. Screening and modulating kinase pathways or developing inhibitors targeting these phosphorylation sites could help restore DJ-1 stability and functionality. Beyond PKAcα, CRISPR screening can identify how other kinases affect DJ-1 dimerization, with BiFC technology enabling real-time monitoring of these changes [41]. This approach will broaden our understanding of DJ-1 regulation and provide potential targets for new therapeutic strategies (Fig. 3 Panel 3).

Molecular chaperones and protein folding

Proper folding of DJ-1 monomers is essential for dimerization, a process assisted by molecular chaperones such as BAG1 (Bcl-2-associated athanogene 1) and BAG2 (Bcl-2-associated athanogene 2). Misfolded DJ-1 proteins, caused by genetic mutations or environmental factors, lead to aggregation or degradation, disrupting dimer formation and reducing functional DJ-1 dimers in neurons. This deficiency is particularly harmful in PD, where the loss of functional DJ-1 dimers heightens neuronal vulnerability to oxidative stress, contributing to disease progression [45]. Experimental evidence suggests that chaperone-based therapy involving BAG1 and BAG2 has shown promising results. For instance, BAG1, as a co-chaperone protein of DJ-1, can promote the dimerization and chaperone function of DJ-1. BAG1 promotes the dimerization of DJ-1, including the PD-linked L166P mutant, and corrects its abnormal subcellular distribution by reducing nuclear accumulation. Functionally, co-expression of BAG1 restores the foldase activity of mutant DJ-1 and reduces cell death caused by the DJ-1 mutation [47]. These findings suggest that BAG1-mediated stabilization of DJ-1 dimers could be a promising therapeutic strategy to enhance neuronal survival in PD. Similarly, Similarly, BAG2 has been shown to directly interact with DJ-1, promoting its dimerization and increasing the dimer-to-monomer ratio, thereby preserving its neuroprotective activity. Overexpression of BAG2 prevents MPP + -induced monomerization of DJ-1, a process associated with PD pathology, and enhances its antioxidative and neuroprotective functions [73]. Targeting BAG1 and BAG2 to stabilize DJ-1 dimerization through gene therapy or small molecules could help mitigate oxidative stress, preserve chaperone function, and reduce neuronal loss in PD (Fig. 3, Panel 4). While experiments show they can restore the function of mutant DJ-1, translating this into clinical practice faces challenges related to delivery, specificity, patient variability, and long-term safety. Effective therapies must overcome these issues, ensuring safe and targeted treatment.

Disruption of these regulatory processes—oxidation, phosphorylation, S-nitrosylation, and chaperone-mediated folding—contributes significantly to the pathogenesis of PD by impairing DJ-1 dimerization. Therapeutic strategies aimed at stabilizing DJ-1 dimers through targeted modulation of these mechanisms (Fig. 3 and Table 2) could mitigate oxidative stress, enhance mitochondrial function, and reduce neuronal death in PD. Future studies should focus on integrating these pathways into a unified therapeutic framework and addressing challenges such as delivery methods and off-target effects.

DJ-1 and mitochondria-targeted therapeutic approaches for PD

Additionally, DJ-1 plays a crucial role in maintaining mitochondrial homeostasis by protecting mitochondria from oxidative stress. Mitochondrial-targeted strategies, including small molecules, chemical chaperones, novel approaches, and drugs in preclinical and clinical stages, are emerging as key therapeutic options aimed at enhancing or stabilizing DJ-1 dimerization(Table 2). DJ-1 interacts with the PINK1/Parkin pathway to regulate mitophagy, thereby protecting mitochondria from damage [56]. Notably, the loss of DJ-1 can be rescued by Parkin overexpression, highlighting a potential therapeutic avenue [74]. Therapies modulating the PINK1/Parkin pathway, including small molecules such as kinetin triphosphate (KTP) to enhance mitochondrial function and clear damaged mitochondria, as well as inhibitors of USP30 (a deubiquitinase that negatively regulates PINK1/Parkin-mediated mitophagy), offer promising strategies to improve mitochondrial health and function [54].

Loss or mutation of DJ-1 leads to mitochondrial dysfunction, increased oxidative stress, and exacerbation of

PD progression. Therefore, enhancing DJ-1 function or stabilizing its dimerization could restore mitophagy and promote the removal of damaged mitochondria. Several small molecules and chemical chaperones, such as phenylbutyrate, have been shown in animal models to enhance DJ-1 expression and mitigate neuronal damage in PD models [60, 61]. Furthermore, DJ-1 is tightly linked to the Nrf2 antioxidant pathway [75]. By activating Nrf2, antioxidant enzyme expression is upregulated, reducing oxidative damage, with DJ-1 acting as a key regulator of this process [75].

In vitro studies have demonstrated that small molecules and natural compounds, including curcumin, celastrol and andrographolide, can activate Nrf2, improving cellular antioxidant capacity and alleviating mitochondrial dysfunction [62]. In PD mouse models, Celastrol enhances mitophagy in the striatum by activating PINK1 and DJ-1 expression, promoting the degradation of damaged mitochondria and inhibiting dopaminergic neuron apoptosis [63]. Andrographolide, similarly, promotes mitophagy through the PINK1/Parkin pathway while enhancing antioxidant defense via Nrf2, providing neuroprotective effect [64]. These mechanisms make Andrographolide a promising adjunctive therapy for PD, particularly for reducing mitochondrial damage and oxidative stress. Additionally, the mitochondria-targeted antioxidant MitoQ (CoQ10) has demonstrated efficacy in both animal models and human studies of PD by protecting mitochondria and reducing oxidative stress [66, 67]. And DJ-1's antioxidant function may complement these therapies to collectively reduce oxidative damage and mitochondrial dysfunction in PD.

These emerging mitochondrial-targeted therapies highlight the potential of enhancing DJ-1 function and stabilizing its dimerization to protect mitochondrial integrity and reduce oxidative stress in PD. By modulating the PINK1/Parkin pathway, small molecules, chemical chaperones, and natural compounds not only improve mitochondrial function but also complement DJ-1's antioxidant role. As such, these therapeutic approaches could serve as valuable adjuncts in PD treatment, paving the way for future clinical applications.

Biomarkers of DJ-1 dimerization: clinical application and therapeutic monitoring

Building on these therapeutic advances, DJ-1 dimerization also holds promise as a biomarker for PD, offering a novel approach for clinical application and therapeutic monitoring. Research indicates that during neurodegeneration, DJ-1 undergoes oxidative modifications, such as carbonylation and methionine oxidation, which lead to the formation of SDS-resistant dimers [15]. These abnormal dimers are associated with impaired DJ-1 function and are found to be elevated in the brains of patients with PD and Alzheimer's disease [76]. Specifically, the accumulation of acidic forms of the monomer and basic forms of the dimer (pI 8.0 and 8.4) has been proposed as a potential biomarker for oxidative stress in these conditions [76]. Furthermore, antioxidants like ascorbate have been shown to significantly reduce the formation of these SDS-resistant dimers [15]. Consequently, monitoring DJ-1 dimerization status could provide a valuable tool for tracking disease progression and evaluating the efficacy of therapeutic interventions.

Studies have also demonstrated that DJ-1 expression levels in body fluids—such as cerebrospinal fluid (CSF), saliva, and plasma—are linked to the onset and progression of PD, the detection of CSF DJ-1 in particular may serve as a potential biomarker for early PD [77–80]. However, to enhance diagnostic accuracy, detection of DJ-1 in body fluids may need to be combined with other biomarkers [81]. We propose that incorporating the monitoring of DJ-1 dimerization alongside DJ-1 levels could offer an effective strategy for tracking disease progression and assessing therapeutic outcomes. Currently, however, research on DJ-1 dimerization is primarily limited to brain tissue samples from PD patients [76], and the difficulty of obtaining such samples restricts its broader clinical application. Therefore, future research should focus on exploring DJ-1 dimer levels in body fluids. Identifying and quantifying DJ-1 dimerization and its oxidative modifications could thus serve as crucial biomarkers for evaluating therapeutic responses in clinical trials, providing a more comprehensive approach to patient management and treatment strategies.

Conclusion and future perspectives

In conclusion, DJ-1 has emerged as a crucial protein in the pathophysiology of PD, primarily through its role in cellular defense mechanisms against oxidative stress. Recent insights into DJ-1 dimerization have further expanded our understanding of its neuroprotective functions, revealing that this process enhances the stability, antioxidative capacity, and cellular resilience of dopaminergic neurons. Additionally, the formation of SDS-resistant DJ-1 dimers may serve as a biomarker for tracking disease progression and evaluating therapeutic efficacy in PD. The molecular dynamics underlying DJ-1 dimerization are critical for modulating its activity, and this intricate regulation offers promising avenues for therapeutic intervention in PD.

While substantial progress has been made in elucidating the mechanistic details of DJ-1's role in PD, several challenges remain. Future research should aim to further characterize the molecular interactions that facilitate DJ-1 dimerization and identify potential small molecules

or compounds that can specifically modulate this process. Additionally, the role of DJ-1 in other neurodegenerative diseases, as well as its potential interactions with other cellular pathways, warrants further exploration. There is also a need for in vivo studies to validate the therapeutic potential of targeting DJ-1 dimerization in preclinical models, and eventually in clinical settings.

The modulation of DJ-1 dimerization represents an exciting frontier in PD research, with the potential to not only slow disease progression but also improve the quality of life for patients. By targeting DJ-1 as a key regulator of neuronal survival, we may be able to develop innovative therapeutic strategies that can address the unmet needs of PD treatment. Continued efforts in this area are essential to uncovering novel neuroprotective approaches, and the exploration of DJ-1 dimer levels in body fluids could offer a comprehensive strategy for evaluating therapeutic responses in clinical trials, providing hope for patients suffering from PD.

Abbreviations

Akt	Protein kinase B
ASK1	Apoptosis signal-regulating kinase 1
ARE	Antioxidant response element
BAG1	Bcl-2-associated athanogene 1
BAG2	Bcl-2-associated athanogene 2
BiFC	Bimolecular fluorescence complementation
CSF	Cerebrospinal fluid
HMW	High molecular weight
KTP	Kinetin triphosphate
PD	Parkinson's disease
Nrf2	Nuclear factor erythroid 2-related factor
PTMs	Post-translational modifications
PI3K	Phosphatidylinositol 3-kinase
PKAcα	Catalytic subunit alpha of protein kinase A
SDS	Sodium dodecyl sulfate

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LLL and WCY conceived and designed the review. LLL reviewed the literature and drafted the manuscript. WCY, TJQ, and ZHN critically revised the manuscript. All authors read and approved the final version of the manuscript.

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Declarations

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Competing interests
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