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Review article

Cytoprotective mechanisms of DJ-1 against oxidative stress through modulating ERK1/2 and ASK1 signal transduction

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ABSTRACT

DJ-1 is a highly conserved multifunctional protein linked to both neurodegeneration and neoplasia. Among its various activities is an antioxidant property leading to cytoprotection under oxidative stress conditions. This is associated with the ability to modulate signal transduction events that determine how the cell regulates normal processes such as growth, senescence, apoptosis, and autophagy in order to adapt to environmental stimuli and stresses. Alterations in DJ-1 expression or function can disrupt homeostatic signaling networks and initiate cascades that play a role in the pathogenesis of conditions such as Parkinson's disease and cancer.

DJ-1 plays a major role in various signaling pathways. Related to its anti-oxidant properties, it mediates cell survival and proliferation by activating the extracellular signal-regulated kinase (ERK1/2) pathway and attenuates cell death signaling by inhibiting apoptosis signal-regulating kinase 1 (ASK1) activation. Here, we review the ways through which DJ-1 regulates these pathways, focusing on how its regulation of signal transduction contributes to cellular homeostasis and the pathologic states that result from their dysregulation.

1. Introduction

DJ-1 is a highly conserved, homodimeric protein that was originally cloned as an oncogene capable of transforming cells in cooperation with activated *ras* [1]. DJ-1 is over-expressed in multiple tumor types and is positively correlated with tumor metastasis and negatively correlated with patient survival [2–8]. Knockdown of DJ-1 sensitizes various tumor cell types to chemotherapeutic drugs [7], demonstrating its crucial role in tumor maintenance. Increased levels of DJ-1 in serum and extracellular fluids have also been proposed as a predictive biomarker in some cancers [9,10] highlighting its potential for cancer diagnosis and prognosis.

While over-expression of DJ-1 in somatic cell lines appears to mediate cancer development, loss of function mutations of DJ-1 in post-mitotic neurons are linked to recessively inherited Parkinson's disease characterized by neuodegeneration of substantia nigra dopaminergic neurons [11]. This places DJ-1 at the center of a nuanced balance where it can regulate cellular processes depending on cell type and serves as a determinant of cell survival or cell death in response to extracellular stimuli.

One way that DJ-1 appears to control cellular homeostasis is through its ability to modulate signal transduction - cell signaling pathways which are able to convey, amplify, and translate the information transmitted from the plasma membrane to the nucleus. For example, DJ-1 can activate the extracellular signal-regulated kinase (ERK1/2) pathway [12,13] and the phosphatidylinositol-3-kinase (PI3K)/Akt pathway [8] to mediate cell survival and proliferation. It can attenuate cell death signaling by inhibiting apoptosis signal-regulating kinase 1 (ASK1) activation [14,15] as well as the mitogen-activated protein kinase kinase kinase 1 (MEKK1/MAP3K1) activation [16] of downstream apoptotic cascades. It also modulates autophagy through many signaling pathways [17–19], a process that can mediate either cell survival or cell death depending on the circumstances [20].

The direct neuroprotective effects of DJ-1 have long been attributed to cysteine residues that sense and attenuate oxidative stress. Its three cysteine residues at Cys46, Cys56, and Cys106 are thought to scavenge reactive oxygen species (ROS) with the quenching activity of their sulfhydryl groups, thereby reducing cellular ROS burden [21]. Cys106, the critical residue considered most susceptible to oxidation, is oxidized to cysteine sulfenic acid (Cys-SOH), cysteine sulfinic acid (Cys-SO_2H), and then cysteine sulfonic acid (Cys-SO_3H) forms, causing the isoelectric point (pI) to shift towards more acidic values. Excessively oxidized Cys106-SO_3H form of DJ-1 is considered inactive, and mutation of Cys106 results in loss of neuroprotective function [22]. The antioxidant activity of DJ-1 is demonstrated by its ability to protect neurons against toxins that increase cellular ROS levels, including H_2O_2, 6-

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OHDA, rotenone and MPTP, in various *in vitro* and *in vivo* studies [18,23–25]. Conversely, knocking down DJ-1 exacerbates the cell death induced by oxidative stress [25–29].

Investigating the function of DJ-1 in cell signaling has been helpful in understanding its function in maintaining cellular homeostasis, and its contrasting roles in neurodegeneration and cancer [30,31]. In this review, we focus on the extracellular signal-regulated kinase (ERK1/2) pathway and the Daxx-apoptosis signal-regulating kinase 1 (ASK1) death signaling pathway as they relate to the anti-oxidant activity of DJ-1.

1.1. Activation of the ERK1/2 pathway by DJ-1

The extracellular signal-regulated kinase (ERK1/2) pathway is a classic mitogen-activated protein kinase (MAPK) signaling cascade that regulates cell proliferation, growth, autophagy, and differentiation. Core pathway members include Ras, Raf, MEK1/2, and ERK1/2 (MAPK) [32,33]. Various stimuli activate this pathway, including growth factors, polypeptide hormones, neurotransmitters, chemokines, and phorbol esters, which bind or activate a variety of receptors and proteins such as receptor tyrosine kinases (RTKs), G-protein coupled receptors (GPCRs), and protein kinase C (PKC) [34].

ERK1/2 are serine-threonine kinases that are positively regulated by MEK1/2-mediated phosphorylation. MEK1/2 are MAPKK proteins with ERK1/2 as their only known physiological substrates [35]. On the other hand, ERK is negatively regulated by a family of dual-specificity (Thr/Tyr) MAPK phosphatases (DUSPs/MKPs) [36]. Activated ERK phosphorylates several downstream transcription factors such as AP-1, c-Jun and c-Myc [37]. ERK can also activate Ribosome S6 Kinase (RSK) and inhibitor kappa-β Kinase (IKK), which can lead to the respective activation of transcription factors cAMP Response Element-Binding (CREB) and Nuclear Factor immunoglobulin Kappa-chain enhancer-β-cell (NF-kappa-β) [35,38].

Several studies have shown that DJ-1 activates ERK1/2, a phenomenon that can contribute to many of the roles that DJ-1 plays in protecting cells from oxidative injury and in regulating gene transcription (Fig. 1).

1.1.1. DJ-1 protects against oxidative injury by activating ERK1/2 and MEK1/2

Several studies have demonstrated that DJ-1 functions upstream of ERK1/2 phosphorylation [12,39–41]. For example, over-expression of wild-type (WT) DJ-1 in COS-7 or MN9D cells up-regulates ERK1/2 and MEK1/2 phosphorylation, while L166P mutant DJ-1, which is linked to Parkinson's disease, cannot enhance ERK1/2 or MEK1/2 phosphorylation [12]. In cancer cell models (T47-D and MCF-7), knock-down of DJ-1 using shRNA leads to down-regulation of phosphorylated ERK1/2 and decreased cell proliferation [42].

In a variety of models, it is well-established that DJ-1 over-expression improves the viability of cells challenged with hydrogen peroxide (H_2O_2) [43,44]. Under these conditions, inhibiting ERK1/2 activation by pretreating cells with the MEK1/2 inhibitor U0126 abolishes the protective effect of WT DJ-1 over-expression. This observation suggests that DJ-1 can protect cells from oxidative injury through activation of the ERK pathway [12].

1.1.2. DJ-1 regulates dopamine (DA) homeostasis through activation of ERK1/2 and the nuclear translocation of Nurr1

One way that DJ-1 may mediate this protective effect is through modulation of Nurr1 levels. The transcription factor Nurr1 plays a major role in dopamine homeostasis. It regulates the expression of dopamine synthetic enzymes tyrosine hydroxylase (TH) and L-dopa decarboxylase (DDC), as well as the expression of vesicular monoamine transporter 2 (VMAT-2), which is necessary for the transport of DA from the cytosol into synaptic vesicles [45–47]. In both *in vivo* and *in vitro* models, DJ-1 has been shown to modulate Nurr1. Over-expression of WT DJ-1 in MN9D cells leads to an increase in the nuclear translocation of Nurr1 as well as an increase in the mRNA levels of Nurr1 target genes. The Parkinson associated pathogenic L166P mutant form of DJ-1, on the other hand, cannot impact Nurr1. As expected, knocking-down DJ-1 expression attenuates the activity of Nurr1 and down-regulates the expression of its target genes [48].

Considering that ERK1/2 increases Nurr1 transcriptional activity [49], it was hypothesized that DJ-1 may regulate Nurr1 activation through the ERK1/2 pathway. Indeed, over-expression of WT DJ-1, but not its L166P mutant, leads to phosphorylation of ERK1/2, and blocking ERK1/2 activation using U0126 prevents DJ-1-mediated nuclear translocation of Nurr1 and the induction of Nurr1 target genes [50]. A similar phenomenon has been shown *in vivo*. Over-expression of WT DJ-1 but not its L166P mutant in the substantia nigra of rats using a lentiviral vector increases ERK activation, Nurr1 nuclear translocation, as well as Nurr1 target protein levels [50].

1.1.3. DJ-1 interacts genetically with ERK1/2

DJ-1 has been shown to interact directly with ERK1/2 [41], and to modulate upstream factors in the MAPK cascade, either through direct interaction or by affecting protein expression [12,13,40].

Mice lacking both DJ-1 and the Glial Neurotrophic Factor (GDNF) tyrosine kinase receptor Ret lose more dopaminergic neurons in the substantia nigra compared to mice lacking only Ret, suggesting a possible cooperation between DJ-1 and Ret [51]. As Ret is upstream of the ERK pathway and necessary for the neuronal survival activity of GDNF [52], a developing *Drosophila* system has been employed to study the effect of DJ-1 on Ret signaling and downstream MAPK pathways. Flies that were made to over-express constitutively active Ret exhibited developmental abnormalities but had unaltered endogenous DJ-1 levels. When these flies were crossed with *Drosophila* expressing reduced DJ-1 levels, the offspring showed complete rescue of the abnormal phenotype. Conversely, when flies expressing constitutively active Ret were crossed with *Drosophila* over-expressing DJ-1, the offspring exhibited more severe developmental defects. These findings indicate a genetic interaction between Ret and DJ-1 in controlling cell size and differentiation [51]. Similarly, DJ-1 interacts genetically with Ras and with ERK/*rolled* (rl), suggesting that DJ-1 may cooperate with Ret, Ras, and ERK during development to control cell differentiation and proliferation [51].

1.1.4. DJ-1 interacts directly with and affects the nuclear translocation of ERK1/2

The transcription factor Elk1 binds to the promoter of the superoxide dismutase (SOD) gene and enhances its expression leading to reduced ROS generation [53]. Elk1 is phosphorylated and activated by MAPK kinases such as ERK1/2 [54], suggesting that one of the mechanisms through which DJ-1 protects cells against ROS is *via* ERK1/2-Elk1 activation leading to SOD induction. Notably, Elk1 activation in the substantia nigra of mice challenged with the mitochondrial complex I inhibitor 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is blunted in DJ-1 KO mice compared to WT mice [41]. However, in contrast to *in vitro* data showing that knocking down DJ-1 reduces ERK1/2 phosphorylation [48], ERK1/2 phosphorylation is not affected in DJ-1 KO mouse brains [41]. This has led to the hypothesis that under oxidative insult, DJ-1 may act as a molecular chaperone [55], to affect the nuclear translocation of ERK1/2 rather than its phosphorylation.

Evidence for direct interaction between DJ-1 and ERK2 has been presented in HEK293T cells and in mouse brain lysates using co-immunoprecipitation [41]. This interaction involves residues 1–100 of DJ-1, but is not impacted by mutation of its cysteine 106, which is necessary for its role as a redox sensor and peroxide scavenger [21,56,57]. Additionally, the nuclear translocation of ERK1/2 is reduced in DJ-1 knock down SH-SY5Y cells and in DJ-1 KO primary mouse neurons [41]. This suggests that DJ-1 promotes the translocation of ERK1/2 to the nucleus upon oxidative stress, allowing ERK1/2 to phosphorylate/

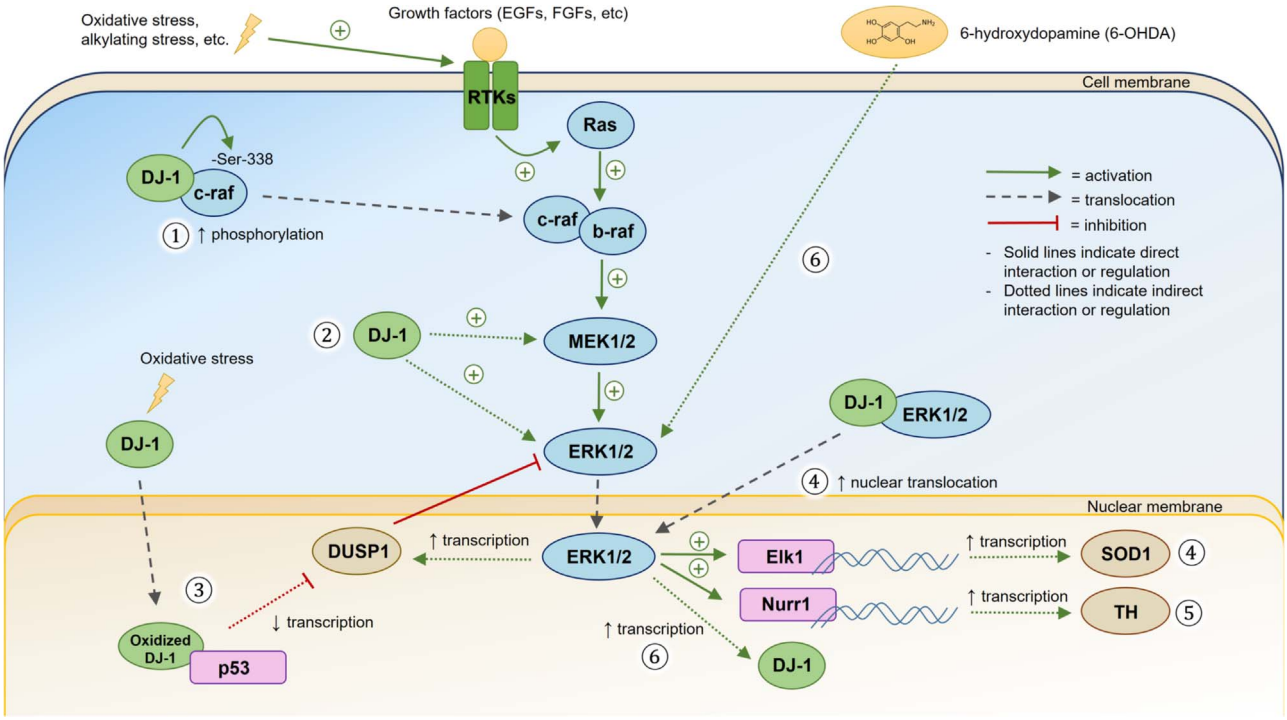

Fig. 1. DJ-1 activates ERK1/2 signaling pathway. (1) DJ-1, but not its C106S mutant, can bind directly to c-Raf and augment c-Raf phosphorylation at Ser-338, which can then activate MEK and ERK1/2 [13]. (2) DJ-1, but not its L166P mutant, protects cells from oxidative injury by activating ERK1/2 and MEK1/2 [12]. The over-expression of wild-type DJ-1 up-regulates ERK1/2 and MEK1/2 phosphorylation [12], while knock-down of DJ-1 down-regulates phosphorylated ERK1/2 [42]. (3) Under oxidative conditions, DJ-1, but not its C106S mutant, sequesters the transcription factor p53 away from promoters, resulting in down-regulation of the ERK1/2 inhibitor, DUSP1 [40]. (4) DJ-1 interacts directly with ERK1/2 and enhances the nuclear translocation of ERK1/2, where it can activate and phosphorylate the transcription factor Elk1, leading to increased transcription of superoxide dismutase (SOD) [41]. (5) DJ-1 modulates dopamine (DA) homeostasis through activation of ERK1/2 and the resulting phosphorylation and activation of the transcription factor Nurr1, which regulates the transcription of tyrosine hydroxylase (TH) [48,50]. (6) Oxidative stress induced by 6-Hydroxydopamine (6-OHDA) may up-regulate DJ-1 through activation of ERK1/2 [24,68]. Positive regulation is indicated by pointed green arrows, and negative regulation is indicated by blunted red arrows. Direct or known regulation is indicated by solid lines; indirect or unknown regulation is indicated by dotted lines. Black dashed arrows indicate translocation. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

activate Elk1, leading to increased SOD expression. This then allows the cell to mount a defense response to suppress the production of superoxide induced by insults such as MPP^+ or paraquat.

1.1.5. DJ-1 binds to and phosphorylates c-Raf, and contributes to activation of the ERK pathway upon EGF stimulation

In addition to reports that DJ-1 may activate ERK1/2 through direct interaction, there is evidence that DJ-1 interacts with c-Raf, a MAPKKK pathway member upstream of ERK1/2 phosphorylation [13,58]. When epidermal growth factor (EGF) binds to its tyrosine kinase receptor (EGFR), it can trigger the activation of Ras, which can then activate c-Raf, a serine/threonine kinase that can phosphorylate MEK, allowing it to activate ERK1/2 [32,33]. EGFR can also be activated by non-physiological stimuli such as oxidants, alkylating agents, and radiation [59,60]. This ligand-independent auto-phosphorylation of EGFR by cellular stressors indicates that ERK pathway activation through this axis is important in oxidant stress induced cellular responses [59].

Pull-down experiments have shown that DJ-1 binds directly to the kinase domain of c-Raf, and this interaction is enhanced upon EGF treatment [13], which augments EGFR and c-Raf activation. Evidence from *in vitro*, cell lines and DJ-1 KO mouse fibroblasts show that, through this binding, DJ-1 modulates the phosphorylation of c-Raf at Ser-338, including increased auto-phosphorylation in a DJ-1 dose-dependent manner, leading to activation of c-Raf and the ERK pathway [13]. Notably, the binding of C106S mutant DJ-1 to c-Raf in pull-down assays is weaker than that of wild-type DJ-1, and the introduction of this mutant into DJ-1 null cells cannot rescue the level of phospho-Ser-338c-Raf to control levels [13]. Since cysteine 106 (Cys106) is highly sensitive to oxidative stress and is essential for the role of DJ-1 as a cytoprotective redox sensor [21,56,57], the latter finding suggests that this ROS-sensing cysteine is important for the interaction of DJ-1 with c-Raf and for subsequent c-Raf activation. Hydrogen peroxide treatment increases highly oxidized sulfinic acid (Cys-SO_2H) and sulfonic acid (Cys-SO_3H) forms of DJ-1 at Cys-106 but fails to increase the level of phospho-Ser-338c-Raf, indicating that these hyper-oxidized and inactive forms of DJ-1 do not aid in the auto-phosphorylation of c-Raf. Additionally, EGF treatment, which increases the level of phospho-Ser-338c-Raf, does not induce DJ-1 oxidation, but subsequent H_2O_2 treatment in EGF-treated cells decreases the level of phospho-Ser-338c-Raf [13]. This suggests that the oxidation of Cys-106 to SO_2H and SO_3H forms is not necessary for the phosphorylation of c-Raf by DJ-1, although the importance of the moderately oxidized sulfenic (Cys-SOH) form of DJ-1 on c-Raf phosphorylation has yet to be elucidated. Thus, although Cys106 residue of DJ-1 appears to be important in the phosphorylation of c-Raf, there remains questions about how oxidative stress may impact the balance between hyperoxidized, oxidized, and unoxidized forms of DJ-1 and the subsequent effect on the level of ERK1/2 activation.

1.1.6. DJ-1 sequesters p53 away from promoters resulting in the down-regulation of ERK1/2 inhibitor, DUSP1

The tumor suppressor p53 is a transcription factor that is activated by cellular stress to induce the expression of genes involved in DNA repair, apoptosis, cell cycle arrest, or autophagy [61,62]. p53 is closely associated with DJ-1 bi-directionally, with evidence showing that DJ-1 represses p53 transcriptional activity to prevent apoptosis [63], while p53 inhibits DJ-1 activation through phosphorylation [64] and decreases DJ-1 protein levels through a post-transcriptional mechanism [65].

Co-immunoprecipitation experiments have shown that p53 binds

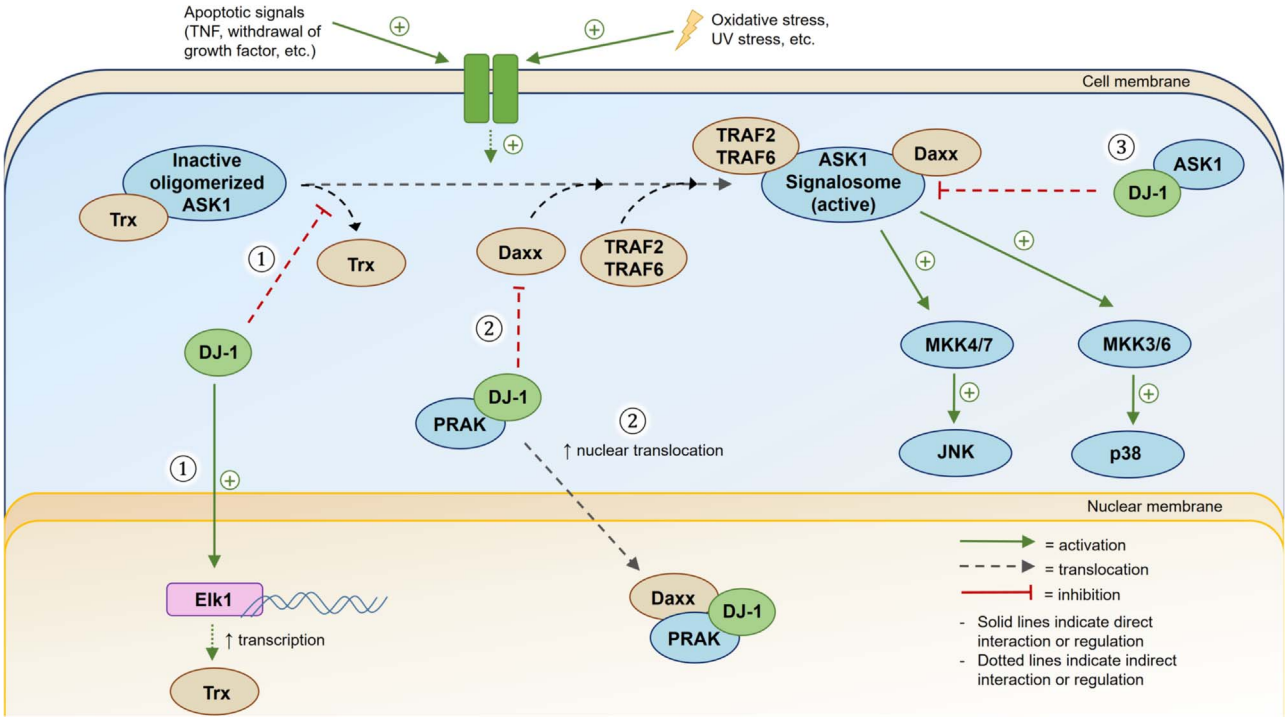

Fig. 2. DJ-1 inhibits the ASK1 pathway. (1) DJ-1 inhibits ASK1 activation by preventing the dissociation of Trx1 from ASK1 and by increasing the transcription of Trx1 [15,23]. (2) DJ-1 inhibits ASK1 activity through nuclear sequestration of Daxx, an ASK1 activator and a part of the active ASK1 signalosome [25,76,82]. Nuclear localization of DJ-1 may occur through its interaction with PRAK/MK5 which contains a nuclear localization sequence (NLS) [83]. (3) DJ-1 may regulate ASK1 activity through direct binding [14,84,91]. Positive regulation is indicated by pointed green arrows, and negative regulation is indicated by blunted red arrows. Direct or known regulation is indicated by solid lines; indirect or unknown regulation is indicated by dotted lines. Black dashed arrows indicate translocation. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

strongly to WT DJ-1 in an oxidative stress dependent manner, whereby their interaction is enhanced following H_2O_2 treatment [40]. The ROS-sensing Cys-106 residue of DJ-1 appears to be necessary for this interaction as C106S mutant DJ-1 fails to co-immunoprecipitate with p53 under oxidative stress. DJ-1 binds to the DNA-binding domain of p53, suggesting that DJ-1 may interfere with the transcriptional activity of p53 [40]. Among other targets of p53, this interaction impacts the expression of DUSP1, which is a mitogen-activated protein kinase phosphatase that can dephosphorylate ERK and regulate apoptosis by inhibiting downstream effectors of the ERK pathway [36].

Hydrogen peroxide challenge of mouse primary fibroblasts leads to increased DUSP1 mRNA and protein expression, which is exaggerated in fibroblasts derived from DJ-1 KO mice, suggesting that DJ-1 may modulate DUSP1 levels [40]. These findings support the notion that under conditions of oxidative stress, DJ-1 forms a complex with p53, sequestering it away from the DUSP1 promoter. Decreased DUSP1 expression then prevents the dephosphorylation of ERK, allowing for the promotion of cell survival under oxidative stress.

1.1.7. DJ-1 can be up-regulated in the context of dopamine-mediated oxidative stress through activation of ERK1/2

While several investigations implicate ERK1/2 activation downstream of DJ-1 signaling, ERK1/2 activation can also up-regulate DJ-1. Challenging human neuroblastoma SH-SY5Y cells with 6-hydroxydopamine (6-OHDA), which leads to increased generation of ROS, is associated with increased DJ-1 levels [66]. Considering that the ERK pathway plays a role in forming a protective response against 6-OHDA-induced stress [67], this up-regulation of DJ-1 is thought to be mediated through ERK. Activation of ERK1/2 in cellular models has been shown to precede the up-regulation of DJ-1 mRNA, while pharmacological inhibition of MEK1/2 attenuates ROS-induced up-regulation of DJ-1 [24,68]. Furthermore, phosphorylation/activation of ERK1/2 occurs in both neuroblastoma cells treated with 6-OHDA and in the striata of mice in which the nigrostriatal pathway is lesioned with 6-OHDA [24,68]. These findings suggest that the interplay between DJ-1, oxidative stress, and the ERK pathway are complex, and that there may be feedback control circuits yet to be elucidated.

1.2. Inhibition of the ASK1 pathway by DJ-1

Apoptosis signal-regulating kinase 1 (ASK1) is a MAPKKK kinase that plays a key role in stress-induced apoptosis, cell survival and differentiation. Downstream of ASK1 are its MAPKKs, mitogen-activated protein kinase kinases (MKK4/MKK7/SEK1 and MKK3/MKK6), which in turn activate c-Jun N-terminal kinases (JNKs) and p38 mitogen-activated protein kinases. This then leads to activation of the mitochondrial cell death pathway to induce apoptosis [33, 69–71].

Under basal conditions, ASK1 is oligomerized through its C-terminal coiled-coil domain and rendered inactive by various inhibitors such as thioredoxin (Trx) [72] and 14-3-3 proteins [73]. Reduced Trx binds ASK1 at its N-terminal coiled-coil domain, and 14-3-3 protein binds ASK1 at its phosphorylated Ser-967 residue [72–74]. These inhibitors regulate ASK1 activation in a redox-sensitive manner and compete with ASK1 activators – such as TNF-alpha receptor associated factors (TRAFs) [74,75] and death-domain associated protein 6 (Daxx) [76].

Upon conditions of cellular stresses such as oxidative stress, ultraviolet (UV) light, endoplasmic reticulum stress, tumor necrosis factor (TNF), and withdrawal of growth factor or serum, phosphorylation of ASK1 at Ser-967 is lost. Daxx then helps release the inhibitory intramolecular interactions between the N- and C- termini of ASK1, and TRAF2 and TRAF6 are recruited to ASK1 to form a larger complex known as the ASK1 signalosome. ASK1 then forms homo-oligomeric interactions through both its C-terminal and N-terminal coiled-coil domains, undergoes auto-phosphorylation at threonine 845, and becomes fully activated [77–81].

DJ-1 inhibits ASK1 activation through various mechanisms

including: (1) sequestration or inhibition of the ASK1 activator, Daxx, (2) direct binding with ASK1, (3) increasing the expression of the ASK1 inhibitor, Trx1, and (4) stabilizing Trx1-ASK1 interaction. These mechanisms lead to inhibition of cell death signaling and the mitochondrial apoptotic cascade, and ultimately promote cell survival (Fig. 2) [14,25,76,82–84].

1.2.1. DJ-1 inhibits ASK1 by sequestering Daxx in the nucleus

The death protein Daxx has been identified in a yeast two-hybrid screen as a DJ-1 interacting protein and subsequently confirmed in co-immunoprecipitation experiments [25]. Over-expression of both Daxx and ASK1 in SH-SY5Y and COS-7 cells increases ASK1 activation and cell death compared with ASK1 over-expression alone. Co-expression of wild-type (WT) DJ-1 in this system represses ASK1 activation and reduces cell death, whereas the Parkinson disease associated L166P DJ-1 mutant cannot protect cells from the effects of Daxx and ASK1 over-expression [25].

Under basal conditions without cellular stress, Daxx is localized mostly in the nucleus while ASK1 is localized in the cytoplasm. Upon cell death signaling, Daxx translocates to the cytoplasm where it interacts with ASK1 to activate apoptosis [78,85]. WT DJ-1 interacts with Daxx in the nucleus and blocks its translocation to the cytoplasm, whereas disease causing L166P and M26I mutant isoforms of DJ-1 fail to interfere with Daxx translocation. Hydrogen peroxide challenge magnifies this phenomenon [25,14]. These findings indicate that WT DJ-1 but not its pathogenic mutants can protect cells against oxidative stress-induced cell death signaling through the Daxx/ASK1 pathway.

In mice, the stress induced by the administration of the mitochondrial complex I inhibitor MPTP also results in the activation of ASK1 signaling and the translocation of Daxx from the nucleus to the cytosol [76,86]. As expected, in ASK1 KO mice exposed to MPTP, nigral dopaminergic neurons are relatively preserved and motor impairment is not as pronounced compared to wild-type littermates [86]. MPTP administration also reduces DJ-1 levels in the ventral midbrain of the animals, particularly in the nuclear fraction, which is consistent with the increased nuclear export of Daxx and its association with and activation of ASK1 in the cytosol [76]. Together, these findings indicate that ASK1 is an effector of oxidative stress-induced toxicity in the brain, and that the cytoprotective function of DJ-1 may be mediated in part by its ability to keep Daxx/ASK1 signaling in check.

DJ-1 also binds to p38 regulated/activated kinase (PRAK/MK5) under cellular stress to help localize DJ-1 into the nucleus, allowing it to sequester Daxx and prevent cell death [83]. PRAK is localized primarily in the cytoplasm under normal conditions, is a downstream effector of the ASK1-MKK3/MKK6-p38 pathway and contains a putative nuclear localization sequence and a nuclear export sequence [87]. DJ-1 has been identified as a PRAK interacting partner in a yeast two-hybrid screen and found to bind directly to PRAK in immunoprecipitation and Fluorescence Resonance Energy Transfer (FRET) assays [83]. DJ-1 also co-localizes with PRAK in the nuclei of NIH3T3 cells under oxidative stress. Following H_2O_2 treatment, PRAK increases phosphorylation and nuclear localization of DJ-1, as well as the nuclear sequestration of Daxx. Conversely, cells lacking PRAK exhibit impaired nuclear localization of DJ-1 and Daxx as well as increased cell death under oxidative stress [83]. Since DJ-1 lacks both a nuclear localization and nuclear export signals, PRAK may be the crucial partner that assists DJ-1 in regulating the cellular localization of Daxx and ASK1 signaling, and hence cell death.

In addition to controlling Daxx localization, DJ-1 modulates Daxx expression through the PI3k/Akt/dFOXO axis. In *Drosophila, DJ-1β* loss-of-function mutants are acutely sensitive to oxidative stress [88,89]. In addition, levels of the Daxx homolog, *Daxx like protein (DLP)* [82] are elevated by H_2O_2, and over-expressing it in neurons renders flies more sensitive to oxidative stress [82]. As Daxx has been shown in mammalian systems to induce apoptosis by activating the JNK/FOXO cell death signaling pathway [78], one study examined the relationship of *DJ-1β* with this pathway. In *DJ-1β* mutant flies, both DLP expression and its translocation from the nucleus to the cytoplasm are increased, whereas over-expressing WT *DJ-1β* reduces the level of endogenous DLP. Furthermore, *DLP* deficiency rescues the phenotypes of *DJ-1β Drosophila* mutants [82]. These findings suggest that, as is the case in mammalian systems, DJ-1β regulates the activity of DLP by limiting its expression and cytosolic localization. Considering that the *DLP* promoter includes a consensus forkhead box subgroup O (FoxO) Response Element (FRE), the transcriptional activity of dFOXO is increased in *DJ-1β* mutant flies, inducing DLP transcription and apoptosis [82]. Interestingly, DLP over-expression also activates the JNK/dFOXO axis in *Drosophila*, and thus, *DLP* activation may further increase *DLP* expression in a feed-forward loop of DLP-JNK-dFOXO [82]. However, the PI3k/Akt pathway, which is also activated by DJ-1, inhibits dFOXO [90]. Thus, *DJ-1β* has a complex role in the regulation of the Daxx homolog DLP, where it modulates its cellular localization and inhibits the activation and over-expression of *DLP*, leading to control of apoptotic signaling through the PI3k/Akt/dFOXO axis.

1.2.2. DJ-1 inhibits ASK1 through direct interaction

In addition to DJ-1 inhibiting the Daxx-ASK1 pathway by binding to Daxx [25], there is some evidence to suggest that DJ-1 may regulate ASK1 activity through direct binding as well [14,84,91]. The two proteins reportedly co-immunoprecipitate upon over-expression. By binding to ASK1, DJ-1 may disrupt ASK1 homo-oligomerization and activation, leading to inhibition of hydrogen peroxide-induced ASK1 activation [84]. Notably, although one study found DJ-1/ASK1 co-immunoprecipitation both in the absence and presence of oxidative stress [84], others have reported that oxidative stress and the resulting oxidized DJ-1 forms are necessary for DJ-1/ASK1 interaction [14,91]. Substitution of Cys-106 residue of DJ-1 to the non-oxidizable alanine (C106A mutant) reportedly abrogates DJ-1/ASK1 interaction, whereas mutations of the peripheral conserved cysteine residues, such as C53A and C46A, still allow the association of DJ-1 with ASK1. This suggests that oxidation of DJ-1 at Cys-106 may be crucial for its binding with ASK1 [14]. Oxidized DJ-1 has also been detected by size exclusion chromatography in native ASK1 complexes that are dissolved upon reducing SDS-PAGE, suggesting that it is incorporated into ASK1 signalosome by mixed disulfide formation dependent on Cys-106 [14]. This mixed disulfide formation is analogous to the interaction between Trx1 and ASK1 at its N-terminal Trx1 binding site. In addition, over-expression of DJ-1 or Trx1 can repress ASK1 homo-oligomerization [84], suggesting that DJ-1 acts similarly to Trx1 in suppressing ASK1 activation. Interestingly, WT DJ-1 is unable to bind ASK1 that lacks this N-terminal Trx1 binding site, but M26I mutant DJ-1 is able to constitutively bind both WT ASK1 and the N-terminal deleted ASK1, presumably at a dysfunctional site [14]. Additionally, while L166P mutant DJ-1 associates with ASK1, the interaction is much weaker than that of wild-type DJ-1 [84]. Unlike WT DJ-1, its C106A, L166P, and M26I mutants fail to protect against oxidative stress [92,93]. This suggests that proper interaction of WT DJ-1 with ASK1, presumably at the N-terminal Trx1 binding site, is necessary for cytoprotection. Parkinson-associated pathogenic DJ-1 mutants, which differ in protein stability and lack normal functionality compared to WT DJ-1, may be unable to properly interact with ASK1, thus contributing to neuronal death.

1.2.3. DJ-1 inhibits ASK1 through Trx1

A third mechanism by which DJ-1 can inhibit ASK1 signaling is through modulating the inhibitory complex of Trx1-ASK1 [15]. Under basal conditions, Trx1 co-immunoprecipitates with ASK1 equally with or without DJ-1 over-expression. However, under oxidative stress, Trx1 dissociates from ASK1, a process that is prevented by over-expression of WT DJ-1, but not its L166P or C106S mutants. Additionally, in DJ-1 KO mouse brain homogenates, the Trx1-ASK1 complex dissociates more readily upon oxidative challenge compared to brains from WT mice, suggesting that DJ-1 plays an important role in the maintenance of the

Trx1-ASK1 inhibitory complex [15]. Additionally, WT DJ-1, but not its L166P or M26I mutants, can up-regulate Trx1 mRNA and protein expression by increasing the levels of the transcription factor Nrf2 and stimulating its translocation to the nucleus [23]. This enhances Nrf2 recruitment to the antioxidant response element (ARE) of the Trx1 gene promoter, increasing the level of Trx1 within the cell and blocking ASK1 activation [23].

2. Conclusion

DJ-1 has emerged as a significant player in major signaling pathways such as ERK1/2 and ASK1, with distinct effects in cancer pathogenesis and neuronal survival. Under oxidative stress, DJ-1 activates the ERK1/2 pathway, which controls the balance of cell proliferation and growth. DJ-1 also inhibits the ASK1 pathway, which plays a key role in stress-induced apoptosis, with overall effects being protection from oxidative injury. However, the majority of studies utilize simple cellular models looking at the effects of various stresses and stimuli. Much of these data need to be confirmed in *in vivo* models where complex cross-talk between various signaling pathways may modulate the overall effects of DJ-1. Nevertheless, a large body of data indicates that DJ-1 impacts the signaling processes that maintain cellular homeostasis under oxidant stress, as well as the delicate balance between premature cell death and uncontrolled proliferation. This suggests the importance of understanding the role of DJ-1 in regulating signal transduction and developing strategies to target it for therapeutic interventions in neurodegeneration and cancer.

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