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Modulation of signaling pathways by DJ-1: An updated overview

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ABSTRACT

Efforts have been made to understand the physiological and pathological role of DJ-1, a Parkinson's disease (PD)-associated protein, to provide new insights into PD pathophysiology. Such studies have revealed several neuroprotective roles of DJ-1, from which its ability to modulate signaling pathways seems to be of utmost importance for cell death regulation by DJ-1. Indeed, research on these topics has led to a higher number of publications disclosing a variety of mechanisms through which DJ-1 is able to modulate signaling pathways in distinct disease-related contexts. Thus, this graphical review presents the most relevant findings concerning the mechanisms through which DJ-1 exerts its regulatory activity on signaling cascades relevant for DJ-1 neuroprotective action, namely ERK1/2, PI3K/Akt, and ASK1 pathways, and Nrf2 and p53 transcription factors-related signaling. A greater focus was given to perform an overview of the research interests over the last years, especially in the most recent works, to highlight the current research lines in this topic, and point out future directions in the field. In addition, the impact of DJ-1 mutations causative of PD and the importance of the redox status of DJ-1's cysteine residues for the action of DJ-1 on signaling modulation was also addressed to uncover the potential pathological mechanisms associated with loss of DJ-1 native function.

Over the years, research has been focusing on studying the physiological and pathological role of DJ-1, a Parkinson's disease (PD)-associated protein, to provide new insights for the understanding of PD [1]. DJ-1 is a homodimeric protein containing three cysteine residues (Cys46, 53, and 106) sensitive to oxidation, providing a crucial role to DJ-1 as an oxidative stress sensor that can coordinate adequate protective responses [2]. Among its multiple functions, DJ-1 is implicated in the regulation of signal transduction mechanisms, responsible for mediating adaptative cellular actions against stress conditions [3] which is of utmost importance to its neuroprotective role (Fig. 1, Table 1 and Supplementary Fig. 1). Therefore, this review focused on the most relevant mechanisms described in the literature (Table 1 and Supplementary Fig. 1) concerning: i) its role in the signaling pathway cascades Extracellular signal-regulated kinase 1/2 (Erk1/2) (Fig. 2), phosphatidylinositol 3-kinase (PI3K)/protein kinase B (PKB, also known as Akt) (Fig. 3) and Apoptosis signal-regulating kinase 1 (ASK1) (Fig. 4); and, ii) its role in the p53 (Fig. 5) and Nrf2 (Fig. 6) transcription factors-related signaling.. To sum up (Fig. 1), the selected studies show that DJ-1 induces cell survival and proliferation by activating ERK1/2 and PI3K/Akt signaling cascades, as well as the Nrf2 pathway-mediated antioxidant response, and attenuates cell death by inhibition of ASK1 and p53-related apoptotic pathways (Fig. 1). The aberrant functioning of the

Abbreviations: AEP, Asparagine endopeptidase; ASK1, Apoptosis signal-regulating kinase 1; Bax, Pro-apoptotic protein Bcl-2 associated X; Cys, Cysteine residue; Daxx, Activator death-associated protein 6; DDC, Dopamine decarboxylase; DUSP1, Dual Specificity Protein Phosphatase 1; Erk1/2, Extracellular signal-regulated kinase 1/2; Fis1, Mitochondrial fission 1 protein; GST, Glutathione-S-transferases; HO-1, Heme oxygenase-1; JNK, c-Jun N-terminal kinase; Keap1, Kelch-like ECH-associated protein 1; MKK3, Mitogen-activated protein kinase kinase 3; NO, nitric oxide; NQO1, NAD(P)H quinone oxidoreductase-1; Nrf2, Nuclear factor erythroid-related 2; Nurr1, Nuclear receptor-related 1; PD, Parkinson's Disease; PI3K/Akt, Phosphatidylinositol 3 -kinase/protein kinase B or Akt; PP2A, Protein phosphatase 2A; PTEN, Phosphatase and tensin homolog; SIRT1, Deacetylase Sirtuin 1; SOD1, Superoxide dismutase-1; VMAT2, Vesicular monoamine transporter 2.

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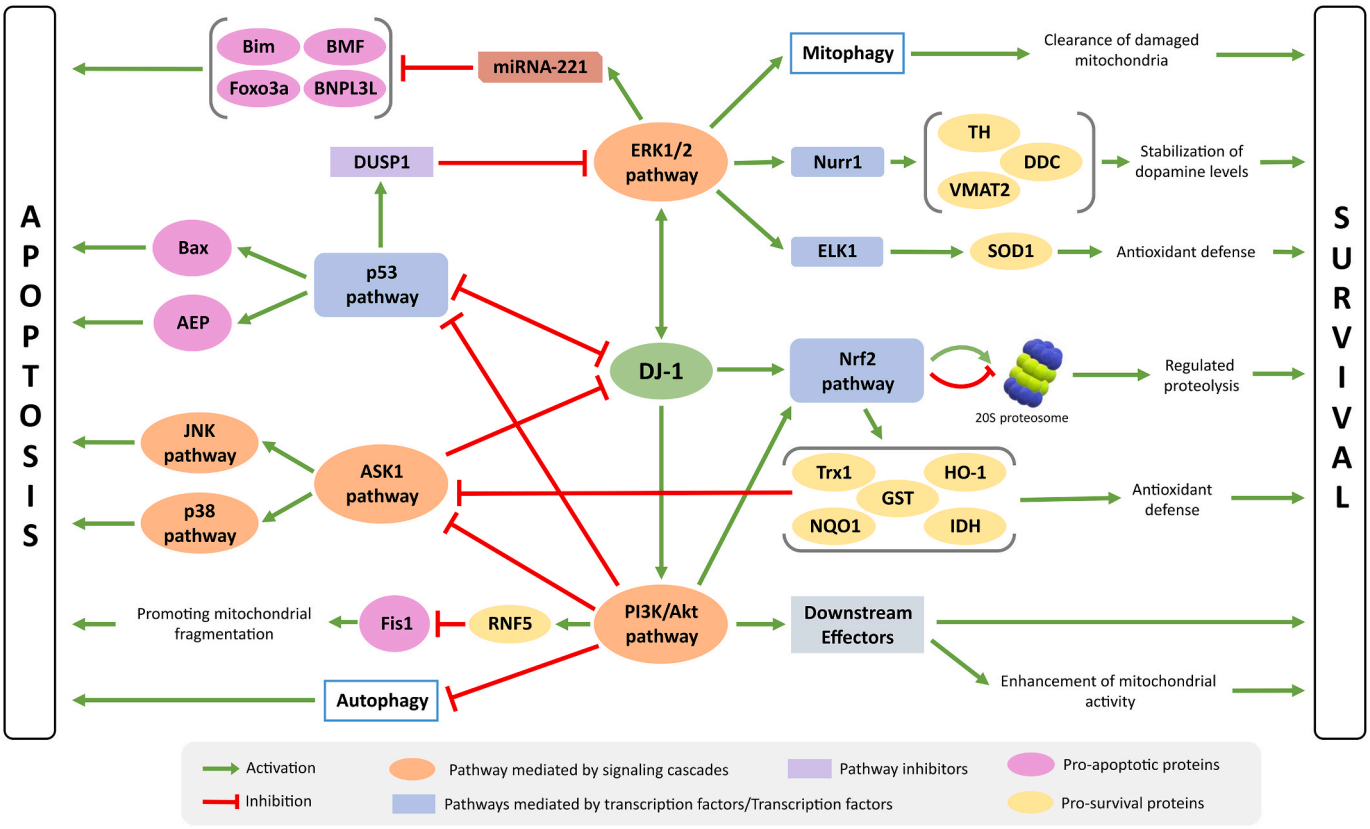

Fig. 1. Overall DJ-1 mechanisms of action of signaling modulation and the respective downstream effects. DJ-1 is able to promote cytoprotective cellular responses towards cell survival while suppressing signaling mechanisms involved in apoptotic events.

mentioned events is known to contribute to the development of multiple diseases, particularly PD. In fact, PD-associated mutations (M26I, L166P, and D149A) of DJ-1 have been shown to lead to the loss of the protective function of the protein, implying the dysregulation of crucial signaling mechanisms (see detailed information in Table 1). Besides, excessive oxidation of the cysteine residues of the protein has also been shown to hinder the native function of DJ-1 on most of the referred pathways. Altogether, these facts reveal the importance of the DJ-1 cysteine residue's redox status, mainly of the central Cys106, and the implication of the PD-related mutant forms in the DJ-1 neuroprotective effect mediated by the regulation of signaling pathways. Moreover, it is clear that DJ-1 is able to modulate the addressed signaling pathways through different mechanisms at various levels, also establishing coordinated signaling networks.

The role of DJ-1 as a signaling mediator has been widely studied over the years. While the major mechanisms of modulation of DJ-1 in the most common pro-survival and cell death signaling pathways seem to have been gradually established throughout the past two decades, an increased interest is denoted in recent years regarding DJ-1 modulation of the Nrf2-mediated antioxidant pathway (Supplementary Fig. 1). Interestingly, the most recent studies have focused on the therapeutic potential of DJ-1, mostly by enhancing Nrf2 signaling as a cytoprotective mechanism in the PD context. Therefore, future research may be expected to increase the potential of DJ-1-mediated therapeutic strategies for PD treatment based on its neuroprotective function led by signaling modulation. Nonetheless, it remains important to determine the basic mechanisms of action of DJ-1 by which the protein can regulate signaling pathways to understand the downstream effects that lead to protective or pathological outcomes.

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Table 1
Overview of the main described DJ-1 functions in signaling regulation and the influence of DJ-1 mutations and importance of cysteine residues.

	Function	Mechanism	DJ-1 activity influenced by						
			PD-related mutations		Cysteine residues		Other mods.	Year	Ref.:
			Which	Effect	Which	Effect			
ERK 1/2 pathway	ERK pathway activation	c-raf binding and stimulation of its self-oxidation on Ser338	–	–	Cys106	Cys106-dependent; but oxidation to SO_2H or SO_3H is not required	–	2015	[4]
		Increase of MEK1/2 and ERK1/2 phosphorylation	L166P	Loss of function	–	–	–	2009	[5]
		Decrease of PP2A levels	L166P	Loss of function	–	–	–		
	Enhancement of pro-survival ERK-dependent mitophagy	–	–	–	–	–	–	2012	[6]
	Upregulation of SOD1 expression levels, enhancing antioxidant response	Interaction with ERK1/2, enhancing its nuclear translocation and phosphorylation of ELK1 transcription factor	–	–	Cys106	Cys106 oxidation not required	–	2011	[7]
	Upregulation of TH, VMAT2, and DDC; dopamine levels stabilization	Enhancement of nuclear translocation and activity of transcription factor Nurr1	L166P	Loss of function	–	–	–	2012, 2016	[8,9]
	ERK1/2-dependent regulation of cytoprotective miRNA-221	Upregulation of miRNA-221 expression levels and activity, leading to the downregulation of pro-apoptotic proteins	M26I	Loss of function	–	–	–	2018	[10]
PI3K/Akt pathway	Akt pathway activation	Promotes Akt phosphorylation	L166P	Loss of function	–	–	–	2010	[13]
			–	–	–	–	–	2005	[14–17]
		Downregulation of PTEN	–	–	–	–	–	2005, 2009, 2014	[14,18, 19]
		Binding and downregulation of PTEN	–	–	Cys106	Requires the presence of the reduced form of Cys106	–	2009	[18]
		Binding and suppression of PTEN activity via transnitrosylation reaction	–	–	Cys106	Cys106-dependent; S-nitrosylation of DJ-1 occurring predominantly at Cys106	–	2014	[19]
		Formation of DJ-1-SG2NA-Akt complex on the mitochondria and plasma membrane	L166P and M26I	L166P - loss of function; M26I - decreased function	Cys106	Cys106-dependent	–	2014	[20]
	Suppression of harmful autophagy	Increase of PTEN and Akt phosphorylation	–	–	–	–	–	2015	[21]
	Improvement of mitochondria activity	Enhancement of Akt phosphorylation	–	–	–	–	–	2016, 2019	[16,17]

(*continued on next page*)

Table 1 (*continued*)

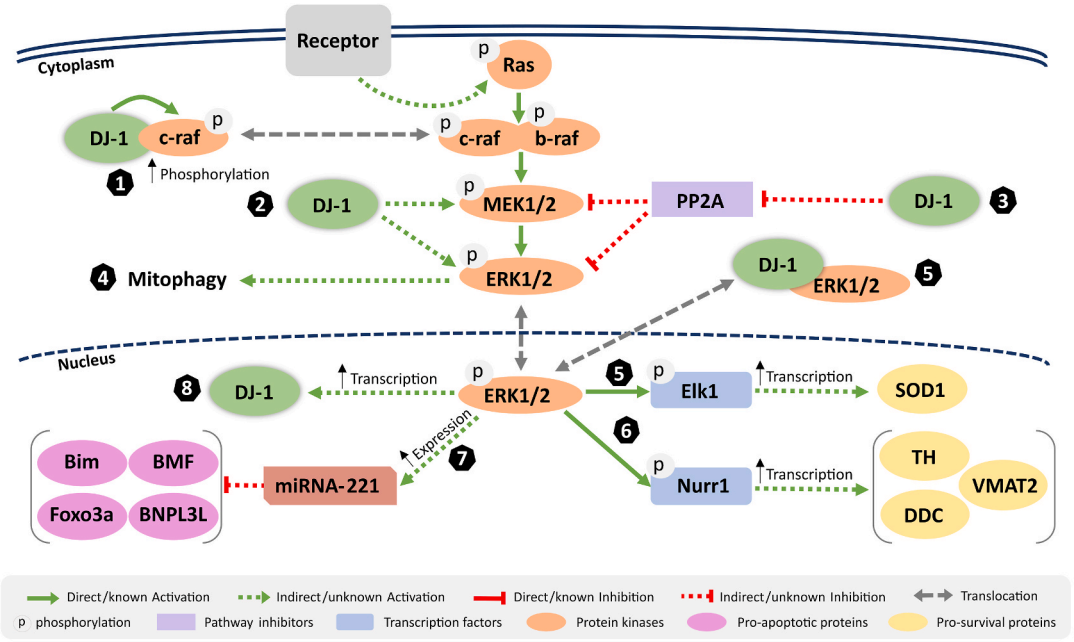
	Function	Mechanism	DJ-1 activity influenced by						
			PD-related mutations		Cysteine residues		Other mods.	Year	Ref.:
			Which	Effect	Which	Effect			
		Degradation of Fis1 via DJ-1/Akt/RNF5 pathway	–	–	Cys106	Cys106 dependent	–	2012	[22]
ASK1 pathway	ASK1 pathway suppression	Prevention of dissociation between ASK1-Trx1	L166P	Loss of function	Cys106	Dependent of Cys106 oxidation	–	2010	[23]
		Suppression of Daxx translocation	–	–	–	–	–	2013	[24]
			M26I	Loss of function	–	–	–	2009	[25]
			L166P	Loss of function	–	–	–	2005	[26]
		Binding and sequestration of Daxx in the nucleus	L166P	Loss of function	–	–	–	2005	[26]
		Suppression of Daxx translocation to the cytoplasm and downregulation of its activity via PI3K/Akt pathway	–	–	–	–	–	2013	[24]
		Interaction with ASK1	M26I	Loss of function	Cys106, Cys53 and Cys46	Cys106 required; Cys53 and Cys46 non-essential but modulate Cys106 activation	–	2009	[25]
		Interaction with ASK1 and disruption of its homo-oligomerization activation	L166P	Loss of function	–	–	–	2010	[28]
	Suppression of ASK1-driven p38 apoptotic pathway	Binding and suppression of ASK1	–	–	Cys106	Cys106-dependent	–	2014	[27]
		Binding and suppression of ASK1, and prevention of MKK3 phosphorylation	–	–	–	–	–	2010	[28]
p53 pathway	p53 activity inhibition	*C*-terminal DJ-1-mediated inhibition of p53 in a PI3K/Akt dependent mechanism	D149A and L166P	Loss of function	–	–	–	2010	[29]
		SUMOylation of DJ- allows its translocation from the nucleus to the cytoplasm and interaction with p53	–	–	–	–	SUMOylation of K130 DJ-1 residue required	2008	[30]
		Binding to p53	–	–	–	–	–	2008	[31]
			–	–	Cys106	Cys106 oxidation dependent	–	2013	[32]
		Enhancement of SIRT1 deacetylase activity upon the acetylated p53	–	–	Cys106	Cys106 dependent	–	2016	[34]
	Downregulation of p53-Bax-caspase apoptotic pathway	Binding to p53	–	–	–	–	–	2008	[31]
		–	–	–	–	–	–	2007	[33]
	Suppression of DUSP1, an ERK pathway inhibitor	Binding to p53	–	–	Cys106	Cys106 oxidation dependent	–	2013	[32]
	Suppression of p53-mediated activation of AEP (legumain)	Binding to the p53 binding site of AEP	–	–	–	–	–	2015	[37]

(*continued on next page*)

Table 1 (*continued*)

	Function	Mechanism	DJ-1 activity influenced by						
			PD-related mutations		Cysteine residues		Other mods.	Year	Ref.:
			Which	Effect	Which	Effect			
Nrf2 pathway	Nrf2 activation	Promoting of Nrf2-Keap1 dissociation, allowing Nrf2 nuclear translocation	–	–	–	–		2006, 2015	[38,39]
		PI3K/Akt-dependent activation mechanism	–	–	–	–	–	2016, 2017, 2019, 2020	[40–43]
		DJ-1 based peptide ND-13 enhancing DJ-1-mediated mechanisms of Nrf2 activation	–	–	–	–	–	2015	[45]
		DJ-1-binding compound B enhances Nrf2 activation through PI3K/Akt pathway by DJ-1-dependent inactivation of PTEN activity	–	–	Cys106	Compound B binds to the Cys106 region of DJ-1, preventing superfluous oxidation	–	2019	[41]
		Other substances (11-Dehydrosinulariolide, Bibenzyl compound 20C, Rosmarinic acid, Cu(II)ATSM, Morinda citrifolia's Active Principle Scopoletin, Tauroursodeoxycholic acid and Salidroside)	–	–	–	–	–	2016, 2017, 2019, 2020	[40, 42–44,46, 48,52]
	Upregulation of NQO1	Enhancing Nrf2 activity	–	–	–	–	–	2006, 2015, 2016 2019	[16,38, 44–47]
	Upregulation of HO-1		–	–	–	–	–	2015, 2016, 2017, 2019, 2020	[16,40, 42–46,48]
	Upregulation of GST		–	–	–	–	–	2018, 2019	[46,49]
	Upregulation of IDH (antioxidant)		–	–	–	–	–	2017	[50]
	Upregulation of Trx1 (ASK1 inhibitor)		L166P and M26I	Loss of function	–	–	–	2012	[51]
	Dual regulation of 20S proteasome activity	20S proteasome activation by enhancing Nrf2 pathway; 20S proteosome inhibition by binding to 20S proteome together with NQO1 enzyme	–	–	Cys106	Cys106 dependent	–	2015	[47]

A)

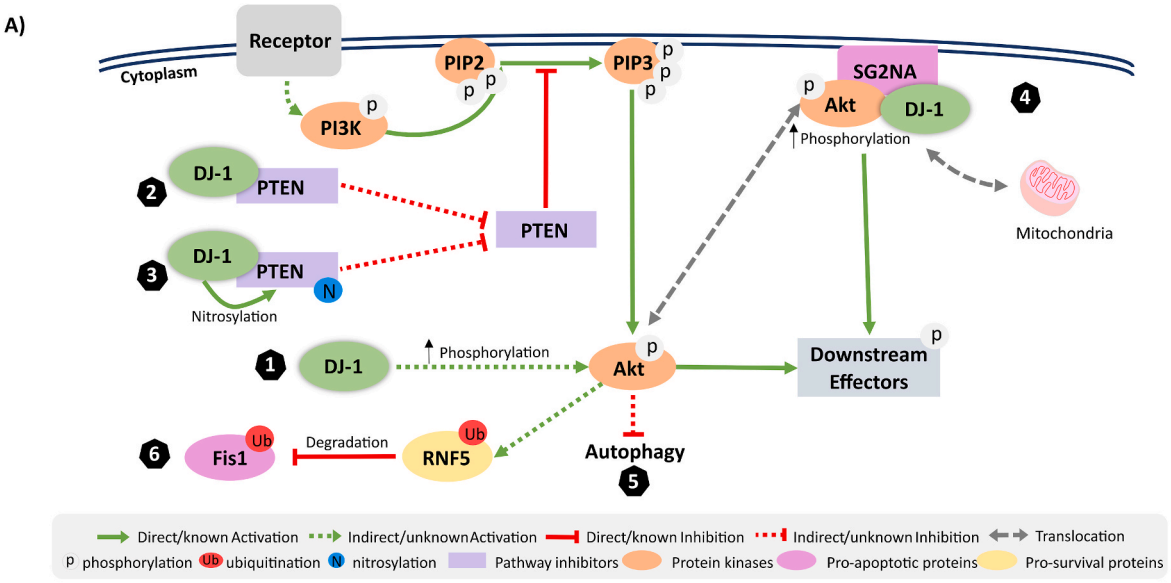


B)

Mechanism/Outcome	DJ-1 activity influenced by				Ref.:
	PD-related mutations		Cysteine residues		
	Which	Effect	Which	Effect	
DJ-1 - c-raf interaction (1)	-	-	Cys106	Cys106-dependent; but oxidation to SO_2H or SO_3H not required	[4]
MEK1/2 and ERK1/2 activation mediated by DJ-1 (2 and 3)	L166P	Loss of function	-	-	[5]
DJ-1 - ERK1/2 interaction (5)	-	-	Cys106	Cys106 oxidation not required	[7]
Nurr1 activation mediated by DJ-1 (6)	L166P	Loss of function	-	-	[8, 9]
miRNA-221expression mediated by DJ-1 (7)	M26I	Loss of function	-	-	[10]

Fig. 2. DJ-1's mechanisms involved in the modulation of the ERK1/2 signaling pathway. A) Schematic representation of the biomolecules, their connections, and the outcomes. (1) DJ-1 is able to bind to c-raf, promoting its self-phosphorylation at Ser338 and activating subsequent pathway components MEK1/2 [4]. In oxidative conditions, phosphorylation of MEK1/2 and ERK1/2 is also increased by a dual-mechanism that includes: (2) the direct action of DJ-1 on these proteins; and (3) the DJ-1 suppression of protein phosphatase 2A (PP2A) expression, a known inhibitor of MEK1/2 and ERK1/2 family kinases [5]. (4) Upon oxidative stress, DJ-1 can promote pro-survival ERK-dependent mitophagy [6]. (5) DJ-1 interacts directly with ERK1/2, enhancing its nuclear translocation. As a result, phosphorylation of downstream transcription factor Elk1 occurs, and the expression of its target protein, superoxide dismutase-1 (SOD1), is increased [7]. (6) DJ-1 enhances nuclear receptor-related 1 (Nurr1) transcription factor activity through activation of the ERK1/2 pathway, triggering the expression of tyrosine hydroxylase (TH), vesicular monoamine transporter 2 (VMAT2), and dopamine decarboxylase (DDC), which are involved in the synthesis and transport of dopamine [8,9]. (7) DJ-1-mediated activation of ERK1/2 signaling promotes miRNA-22 neuroprotective function by enhancing its expression, in turn downregulating the expression of pro-apoptotic proteins, such as bcl-2-like protein 11 (Bim), bcl2 modifying factor (BMF), forkhead box O3 (Foxo3a) and bcl2 interacting protein 3-like (BNPL3L) [10]. (8) Finally, ERK1/2 pathway can also be responsible for upregulating DJ-1 upon stress stimuli, generating a loop regulatory mechanism [11] (Adapted from reference [12]). **B)** The influence of DJ-1 mutations and the importance of DJ-1 cysteine residues in the protein's signaling regulation mechanisms.

A)

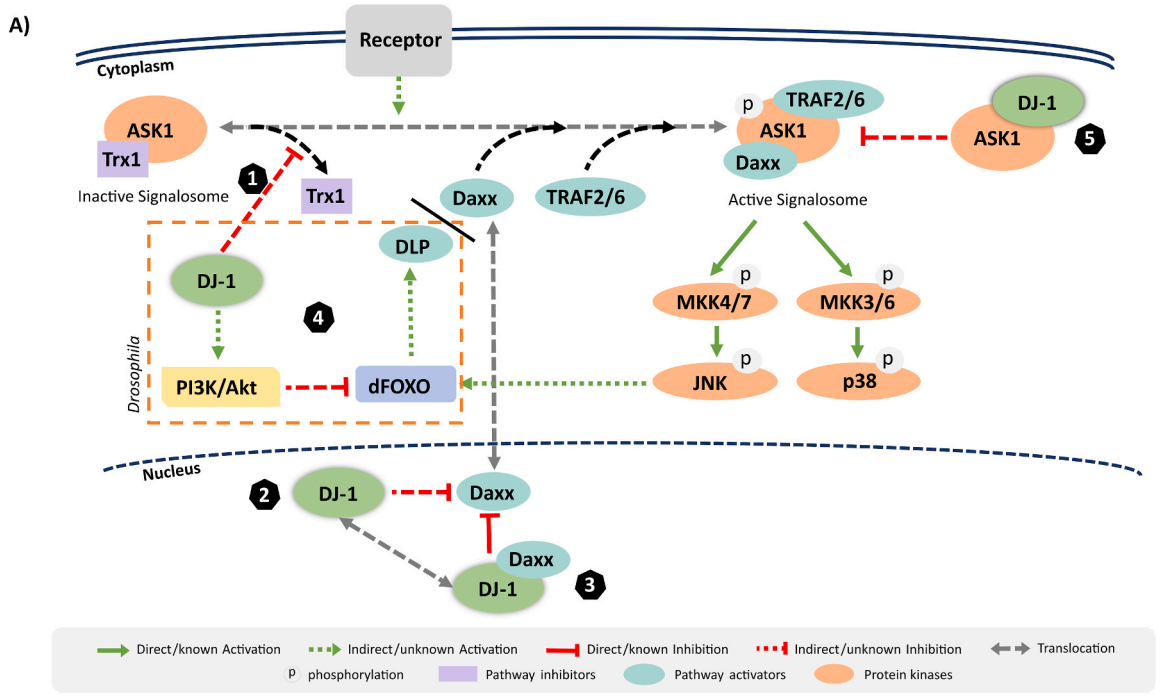


B)

Mechanism/Outcome	DJ-1 activity influenced by				Ref.:
	PD-related mutations		Cysteine residues		
	Which	Effect	Which	Effect	
Akt activation mediated by DJ-1 (1)	L166P	Loss of function	-	-	[13]
DJ-1 – PTEN interaction (2)	-	-	Cys106	Requires the presence of the reduced form of Cys106	[18]
PTEN nitrosylation mediated by DJ-1 (3)	-	-	Cys106	Cys106-dependent; S-nitrosylation of DJ-1 occurring predominantly at Cys106	[19]
DJ-1-Akt-SG2NA complex formation (4)	L166P and M26I	L166P - loss of interaction; M26I - decreased interaction	Cys106	Cys106-dependent	[20]
Fis1 degradation mediated by DJ-1 (6)	-	-	Cys106	Cys106-dependent	[22]

Fig. 3. DJ-1's mechanisms involved in the modulation of PI3K/Akt pathway. A) Schematic representation of the proteins, their connections, and the outcomes. (1) DJ-1 promotes phosphorylation of Akt, enhancing protective responses executed by the downstream effectors, having an effect, for instance, in mitochondrial well-functioning [13–17]. On the other hand, DJ-1 can suppress the PI3K/Akt pathway inhibitor's activity, phosphatase and tensin homolog (PTEN) protein, (2) by binding to it [18] or (3) by establishing a nitrosylation reaction upon mild nitrosative conditions [19]. (4) The interaction between DJ-1 and Akt may be promoted by the S/G2 nuclear autoantigen (SG2NA), forming a complex by recruiting DJ-1 and Akt mainly to mitochondria and plasma membrane, promoting Akt signaling activity [20]. (5) Defensive responses induced by DJ-1-dependent activation of PI3K/Akt pathway include the prevention of harmful autophagy processes caused by C2-ceramide insults [21]. (6) Finally, PI3K/Akt pathway activation mediated by DJ-1 is also involved in the proteasomal degradation of mitochondrial fission 1 (Fis1) protein responsible for mitochondrial fragmentation, by targeting RING-finger protein-5 (RNF5) ligase activity [22]. **B)** The influence of DJ-1 mutations and the importance of DJ-1 cysteine residues in the protein's signaling regulation mechanisms.

A)

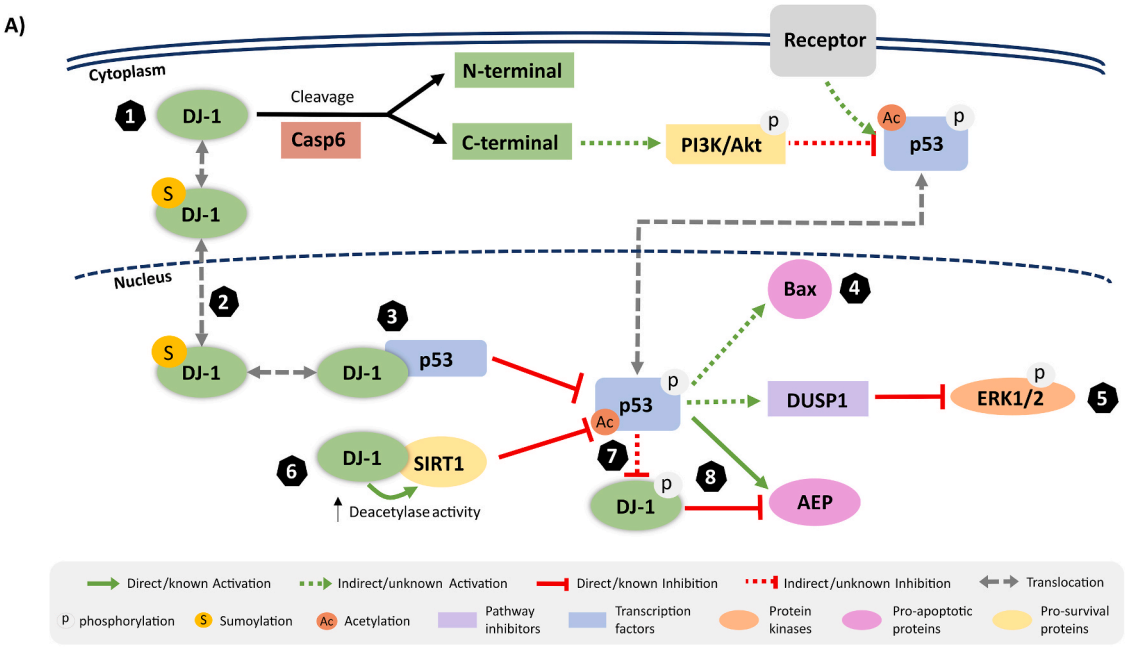


B)

Mechanism/Outcome	DJ-1 activity influenced by				Ref.:
	PD-related mutations		Cysteine residues		
	Which	Effect	Which	Effect	
Prevention of dissociation between ASK1-Trx1 (1)	L166P	Loss of function	Cys106	Dependent of Cys106 oxidation	[23]
Suppression of Daxx translocation (2)	M26I	Loss of function	-	-	[25]
DJ-1-Daxx interaction (3)	L166P	Loss of function	-	-	[26]
DJ-1-ASK 1 interaction (5)	M26I	Loss of function	Cys106, Cys53 and Cys46	Cys106 required; Cys53 and Cys46 non-essential but modulate Cys106 activation	[25]
	-	-	Cys106	Cys106-dependent	[27]
	L166P	Loss of function	-	-	[28]

Fig. 4. DJ-1's mechanisms involved in the modulation of the ASK1 pathway. A) Schematic representation of the proteins, their connections, and the outcomes. (1) DJ-1 prevents the dissociation of the ASK1 inhibitor, thioredoxin 1 (Trx1), from the inactive signalosome, inhibiting activation of the ASK1-induced c-Jun *N*-terminal kinase (JNK) and p38 apoptotic pathways [23]. (2) DJ-1 can suppress the translocation of the ASK1 activator death-associated protein 6 (Daxx) to the cytoplasm and prevent the formation of the active ASK1 signalosome [24,25]. (3) In fact, under oxidative stress conditions, DJ-1 is able to interact directly with Daxx, sequestering the protein in the nucleus and ensuring cell survival [26]. (4) A study conducted in *Drosophila* indicated that DJ-1 also suppressed Daxx like protein (DLP) interaction with ASK1, by downregulating the activity of enhancer forkhead box subgroup O (dFOXO) in a PI3K/Akt signaling-dependent manner [24]. (5) Upon oxidative stimulation, DJ-1 may also interact directly with ASK1 [25,27,28] and suppress p38 and JNK-induced cellular apoptosis, in part by disrupting the homo-oligomerization type of activation of ASK1 [28] (Adapted from reference [12]). **B)** The influence of DJ-1 mutations and the importance of DJ-1 cysteine residues in the protein's signaling regulation mechanisms.

A)

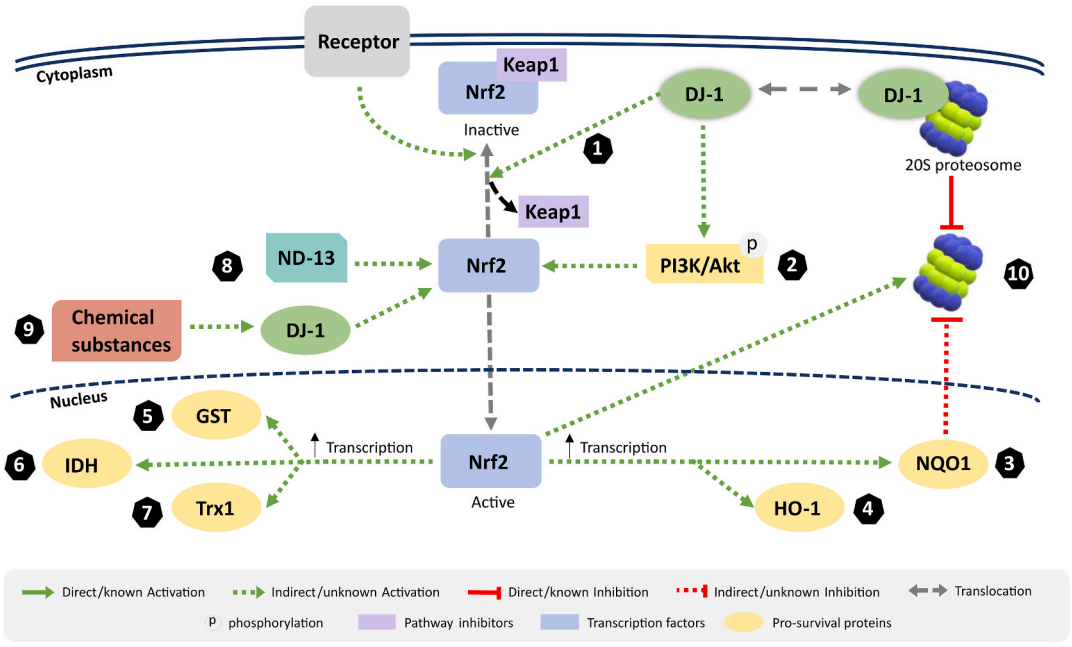


B)

Mechanism/Outcome	DJ-1 activity influenced by					Ref.:
	PD-related mutations		Cysteine residues		Other modifications	
	Which	Effect	Which	Effect		
C-terminal DJ-1-mediated inhibition of p53 (1)	D149A and L166P	Loss of function	-	-	-	[29]
DJ-1-p53 interaction (2 and 3)	-	-	Cys106	Cys106 oxidation dependent	SUMOylation of K130 DJ-1 residue required for DJ-1 translocation	[30] [32]
Suppression of DUSP1 (5)	-	-	Cys106	Cys106 oxidation dependent	-	[32]
Enhancement of SIRT1 deacetylase activity (6)	-	-	Cys106	Cys106 dependent	-	[34]

Fig. 5. A) DJ-1's mechanisms involved in p53 pathway regulation. A) Schematic representation of the proteins, their connections, and the outcomes. (1) The DJ-1 *C*-terminal generated by caspase-6 proteolysis is able to repress p53 activity in a PI3K/Akt-dependent manner [29]. (2) Studies indicate that a proper sumoylation of DJ-1 is required for the nuclear localization of the protein and subsequent suppression of the p53 apoptotic pathway [30]. (3) In the nucleus, DJ-1 can bind to p53 and inhibit its transcriptional activity [31,32]. Consequently, the expression of p53-related targets, such as (4) the Bcl-2 associated X (Bax) apoptotic protein [31,33] and (5) the Erk1/2 inhibitor Dual Specificity Protein Phosphatase 1 (DUSP1) [32] are suppressed, resulting in the inhibition of apoptosis. (6) Moreover, the interaction between DJ-1 and Sirtuin 1 (SIRT1), enhances the deacetylase activity of SIRT1 towards p53 inactivation [34]. (7) Conversely, p53 has been shown to have a downregulatory effect on DJ-1 expression and mRNA levels, besides targeting the protein for an inhibitory phosphorylation reaction [35,36]. (8) Tumor suppressor p53 is also responsible for the increase of neurotoxic asparagine endopeptidase (AEP) activity. DJ-1 is able to suppress this p53-mediated activation of AEP by binding to its p53 binding site [37]. **B)** The influence of DJ-1 mutations and the importance of DJ-1 cysteine residues in the protein's signaling regulation mechanisms.

A)



B)

Mechanism/Outcome	DJ-1 activity influenced by				Ref.:
	PD-related mutations		Cysteine residues		
	Which	Effect	Which	Effect	
Nrf2 activation through PI3K/Akt pathway (2)	-	-	Cys106	Overoxidation of Cys106 oxidation inhibits DJ-1 activity	[41]
Upregulation of Trx1 (7)	L166P and M26I	Loss of function	-	-	[51]
Dual regulation of 20S proteasome activity (10)	-	-	Cys106	Cys106 dependent	[47]

Fig. 6. DJ-1's mechanisms involved in Nrf2 pathway regulation. A) Schematic representation of the proteins and chemical substances, their connections, and the outcomes. (1) DJ-1 stabilizes Nrf2 by favoring Nrf2 free form, possibly by promoting the dissociation from its inhibitor, the Kelch-like ECH-associated protein1 (Keap1) [38,39]. (2) DJ-1 is also able to modulate Nrf2 signaling, activating it in a PI3K/Akt-dependent manner [40–43]. As a result of the DJ-1-mediated activation of the pathway, nuclear Nrf2 triggers the expression of specific enzymes involved in antioxidant responses, such as (3) NAD(P)H quinone oxidoreductase-1 (NQO1) [16,38,44–47], (4) heme oxygenase-1 (HO-1) [16,40,42–46,48], (5) Glutathione S-transferase (GST) [46,49] (6) Isocitrate dehydrogenase (IDH) [50] and (7) Trx1 [51]. (8) The DJ-1 based peptide ND-13 is a DJ-1 and TAT-based peptide with therapeutic potential, promoting DJ-1-dependent activation of Nrf2 antioxidant mechanism [45]. (9) Several chemical substances (11-Dehydrosinulariolide [40], Compound B [41], Bibenzyl compound 20C [42], Rosmarinic acid [43], Cu(II) ATSM [44], Morinda citrifolia's Active Principle Scopoletin [46], Tauroursodeoxycholic acid [48] and Salidroside [52]) have also been described with a promising effect in enhancing DJ-1-mediated Nrf2 signaling activation. (10) Furthermore, DJ-1 is involved in a loop regulatory mechanism of the 20S proteasome that provides a balance in protein degradation processes. DJ-1 may bind to 20S proteasome, inhibiting its action together with NQO1 enzyme. Contrarily, the DJ-1-mediated Nrf2 activation also leads to 20S proteasome enhancement [47]. **B)** The influence of DJ-1 mutations and the importance of DJ-1 cysteine residues in the protein's signaling regulation mechanisms.

Authors' contributions

MN. Investigation, writing—original draft preparation, preparation of tables, and figure design; SIA, BM, MG. Conceptualization, reviewed and edited. All authors have read and agreed to the final version of the manuscript.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.redox.2022.102283.

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