Neurobiology of Disease 108 (2017) 65–72

Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

Review

Recent findings on the physiological function of DJ-1: Beyond Parkinson's disease

Alice Biosa [a], Federica Sandrelli [b], Mariano Beltramini [a], Elisa Greggio [a], Luigi Bubacco [a], Marco Bisaglia [a,*]

[a] Molecular Physiology and Biophysics Unit, Department of Biology, University of Padova, 35131 Padova, Italy
[b] Neurogenetics and Chronobiology Unit, Department of Biology, University of Padova, 35131 Padova, Italy

ARTICLE INFO

Article history:
Received 26 April 2017
Revised 26 July 2017
Accepted 16 August 2017
Available online 18 August 2017

Keywords:
Antioxidant response
Copper chaperone
Gene transcription
Glycating stress
Glyoxalases
Oxidative stress
Parkinson's disease
SOD1 maturation

ABSTRACT

Several mutations in the gene coding for DJ-1 have been associated with early onset forms of parkinsonism. In spite of the massive effort spent by the scientific community in understanding the physiological role of DJ-1, a consensus on what DJ-1 actually does within the cells has not been reached, with several diverse functions proposed. At present, the most accepted function for DJ-1 is a neuronal protective role against oxidative stress. However, how exactly this function is exerted by DJ-1 is not clear. In recent years, novel molecular mechanisms have been suggested that may account for the antioxidant properties of DJ-1. In this review, we critically analyse the experimental evidence, including some very recent findings, supporting the purported neuroprotective role of DJ-1 through different mechanisms linked to oxidative stress handling, as well as the relevance of these processes in the context of Parkinson's disease.

Contents

1. Introduction

In 2003, Bonifati and colleagues discovered that mutations in DJ-1 are associated with an early onset, recessive form of Parkinson's disease (PD) (Bonifati et al., 2003). Since then, enormous efforts have been put

* Corresponding author.
E-mail address: marco.bisaglia@unipd.it (M. Bisaglia).
Available online on ScienceDirect (www.sciencedirect.com).

http://dx.doi.org/10.1016/j.nbd.2017.08.005
0969-9961/

to understand DJ-1 pathobiology. DJ-1 is a dimeric, ubiquitous protein of 189 amino acids, whose PD pathological variants have been associated with loss of function (Bonifati et al., 2003). Even though DJ-1 has been implicated in different cellular processes, including homeostatic control of reactive oxygen species (ROS), transcription regulation, protein folding, modulation of glucose levels, fertility and cellular transformation, a role in neuronal protection against oxidative stress seems the most widely accepted (Cookson, 2012). In agreement with this, overexpression of DJ-1 results in neuronal cytoprotection against oxidative damage, whereas DJ-1 deficiency leads to an increase of oxidative stress-induced cell death, both in cell culture and animal models (Batelli et al., 2015; Kim et al., 2005b; Meulener et al., 2005; Ottolini et al., 2013; Taira et al., 2004; Thomas et al., 2011). Unfortunately, the molecular mechanisms underlying DJ-1 function remain elusive.

DJ-1 possesses three cysteine residues: C46, C53 and C106. Among them, C106 is highly conserved in mammals and can be oxidized (Canet-Aviles et al., 2004; Kinumi et al., 2004; Wilson et al., 2003) and converted into cysteine-sulfenic, -sulfinic and -sulfonic acids. The great interest in this specific amino acid arises from the fact that it seems to render DJ-1 a sensor of oxidative stress. Indeed, C106 appears essential for DJ-1 antioxidant activity (Canet-Aviles et al., 2004; Meulener et al., 2006; Taira et al., 2004), since the substitution with any other amino acid usually inhibits its neuroprotective function. Of note, the other two cysteine residues, C46 and C53, localized at the interface of the two DJ-1 monomers, have also been proposed to be redox-sensitive (Waak et al., 2009).

While several review articles thoroughly discussed the purported functions of DJ-1 (Ariga et al., 2013; Cookson, 2010; Cookson, 2012), recent experimental data highlight novel molecular mechanisms that may account for the antioxidant properties of DJ-1. This review will focus on the recent evidence supporting a neuroprotective role of DJ-1 through regulation of gene transcription, copper transfer to superoxide dismutase 1 (SOD1), deglycase and glyoxalase activity, as well as the relevance of these processes in the context of PD.

1.1. Regulation of gene expression

DJ-1 has been suggested to orchestrate different cellular pathways involved in the response to oxidative stress. In fact, DJ-1 expression is upregulated under oxidative stress conditions and the protein translocates into the nucleus upon exposure to stress, suggesting a key role in gene transcription (Kim et al., 2012). It is worth mentioning that DJ-1 does not exhibit any distinct DNA-binding domain suggesting it likely acts as a co-activator of transcription (Yamaguchi et al., 2012).

Five different signalling pathways, which have been suggested to be controlled by DJ-1, will be discussed here (Fig. 1): the Extracellular Signal-regulated Kinase/ETS domain-containing protein (ERK/Elk), the Nuclear factor E2-Related Factor 2 (Nrf2), PhosphoInositide 3-Kinase/Protein Kinase B (PI3K/PKB), p53 and Apoptosis Signal-regulating Kinase 1 (ASK1) signalling cascades. They all have important roles in cell survival, antioxidant defence and response to cellular stress.

1.1.1. The ERK/Elk pathway

DJ-1 is proposed to be involved in the ERK/Elk pathway, which stimulates cell survival in presence of several stimuli, such as Tumor Necrosis Factor (TNF), growth factor withdrawal and nitric oxide (Erhardt et al., 1999; Kim et al., 2002; Tran et al., 2001). Interestingly, Wang et al. (2011) observed that, upon oxidative stress, DJ-1 helps ERK1/2 to translocate into the nucleus, where it phosphorylates Elk. Elk is a transcription factor that controls the expression of genes involved in the antioxidant defence, including *SOD1* (Wang et al., 2011). Accordingly, DJ-1 overexpression in murine MN9D dopaminergic cells is protective against rotenone-induced oxidative stress and this beneficial effect is blocked by the ERK pathway inhibitor U0126, suggesting a link between the DJ-1 function and ERK/Elk signalling cascade (Gao et al., 2012). On the other hand, DJ-1 knock-down has been associated with a reduction of ERK1/2 nuclear distribution and a consequent decrease in both the nuclear amount of pElk1 and levels of SOD1 protein. In addition, the DJ-1 L166P pathological variant is not able to activate the ERK/Elk pathway, possibly explaining its inability to counteract oxidative stress (Gu et al., 2009). Of note, oxidation of C106 is not necessary for DJ-1 binding to ERK1/2, since DJ-1 C106A overexpression restores ERK1/2 nuclear translocation and is neuroprotective against oxidative insults in murine *DJ-1* null neurons (Wang et al., 2011).

1.1.2. The Nrf2 pathway

DJ-1 has also been reported to modulate the activity of Nrf2 transcription factor, the master regulator of the antioxidant response (Gorrini et al., 2013). DJ-1 favours the dissociation of Nrf2 from its inhibitor Kelch-like ECH-Associated Protein 1 (Keap1), thus promoting Nrf2 nuclear translocation and the expression of its target genes (Clements et al., 2006; Yan et al., 2015). Accordingly, in H157 non-small-cell lung

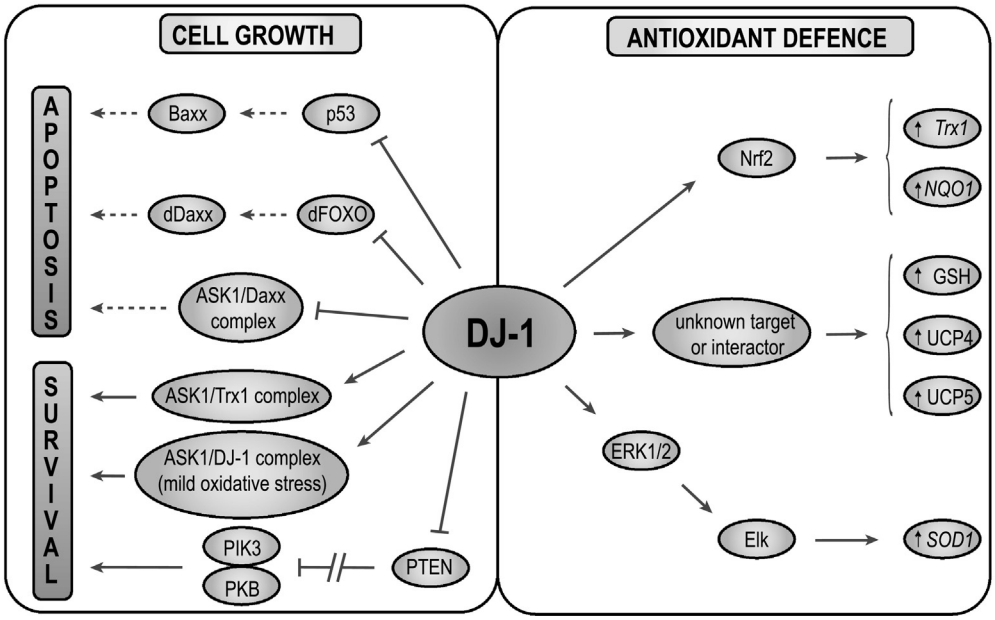

Fig. 1. Summary of the gene expression pathways regulated by DJ-1. These pathways are involved in antioxidant defence or in cell survival. See text for details.

carciroma cells *DJ-1* silencing reduces the expression of several Nrf2-regulated genes, including *NAD(P)H quinone dehydrogenase 1 (NQO1)* (Clements et al., 2006). In the same work, it has been proposed that the function of DJ-1 as transcriptional regulator relies on the presence of the antioxidant responsive element (ARE) in the promoter region of Nfr2 target genes. Although a direct binding between DJ-1 and ARE elements is unlikely, L166P and M26I DJ-1 pathological variants, in contrast to the wild-type DJ-1 form, are not able to induce the expression of Thioredoxin 1 (Trx1), an oxidoreductase element involved in cellular antioxidant defence carrying an ARE signal in its promoter (Im et al., 2012). An additional piece of evidence confirming the role of DJ-1 in this pathway in cells and *in vivo* comes from a very recent paper where the authors showed that $Cu^{(II)}$ATSM treatment in human cardiac myocytes and in human coronary artery smooth muscle cells activates Nrf2 cascade and the antioxidant defence *via* DJ-1 (Srivastava et al., 2016). This paper, in addition to the previous works, shed light on a new level of complexity in the signalling, which is represented by the binding of DJ-1 to the copper metal ion. Intriguingly, in 2012 Gan et al. (2010) showed that the Nrf2 activation pathway is independent from DJ-1 presence in mice brain and primary astrocytes, raising the possibility that the link between DJ-1 and the Nrf2 is tissue-specific. On the other hand, in 2015, Lev and colleagues demonstrated that in SH-SY5Y cells the DJ-1-based peptide ND-13 can stimulate the Nrf2 cascade, suggesting that primary astrocytes cultures and immortalized cells could have different preferential signalling cascades (Lev et al., 2015).

1.1.3. The PI3K/PKB (Akt) pathway

Another transcription pathway possibly modulated by DJ-1 is the PI3K/PKB (Akt) transduction cascade, one of the major pathways controlling cell growth (Kumar et al., 2011). In particular, the Phosphatase and TENsin homologue deleted from chromosome 10 (PTEN), a key player in this pathway, can repress PIK3 kinase activity in absence of cell survival stimuli, preventing both phosphatidylinositol 3,4,5-trisphosphate formation and PKB activation (Salmena et al., 2008). In this pathway, DJ-1 has been described as preventing PTEN repression function in both *Drosophila* eye and mammalian cells (Kim et al., 2005a; Kim et al., 2009), by binding to PTEN and repressing its phosphatase activity (Kim et al., 2009). As a consequence, this leads to the stimulation and activation of PI3K and PKB phosphorylation, favouring cell survival. Interestingly, Kim and colleagues showed that PTEN and DJ-1 co-localize and their interaction is enhanced in the presence of oxidizing stimuli compared to normal conditions, suggesting that the oxidative status of DJ-1 plays a key role in stimulating cell growth (Kim et al., 2009). Specifically, in cells challenged with H_2O_2, PTEN was inhibited by DJ-1 in a time-dependent manner, because of the oxidative status of DJ-1, emphasizing the importance of DJ-1 as a sensor of oxidative stress in the modulation of cell survival. This paralleled with increased levels of phospho-PKB under oxidizing conditions, confirming the role of DJ-1 in the activation of this pathway.

1.1.4. The p53 pathway

Under oxidative stress p53 transcription factor is phosphorylated, translocates into the nucleus and stimulates the apoptotic response to prevent accumulation of DNA damage (Ashcroft et al., 2000). Recently, it has been proposed that DJ-1 is able to interact with the DNA-binding region of p53 protein and to inhibit its pro-apoptotic function. Interestingly, the association between DJ-1 and p53 is dependent on the redox state of DJ-1 C106 residue (Kato et al., 2013), further highlighting the importance of DJ-1 as redox sensor to suppress apoptosis under oxidative conditions. In addition, DJ-1 could control the protein levels of some transcriptional targets of p53, such as the apoptosis regulator BCL2-Associated X protein (Bax). In fact, by decreasing *Bax* expression, DJ-1 induces cell survival in a redox-dependent manner (Fan et al., 2008). In contrast, the L166P DJ-1 pathological mutant interferes with B-Cell lymphoma-eXtra Large (Bcl-xL)/Bax heterodimerization, which is one of the molecular mechanisms to inhibit cell death, thus promoting apoptosis (Ren et al., 2012).

1.1.5. The ASK1 pathway

DJ-1 has also been proposed as a regulator of the ASK1 pathway, which is essential in the regulation of cellular responses to different stressing stimuli, such as redox imbalance, calcium influx, lipopolysaccharide exposure and endoplasmic reticulum stress (Liu et al., 2013). More specifically, under oxidative stress conditions, the binding of DJ-1 to ASK1 and the death domain-associated protein 6 (Daxx) precludes the interaction between these two proteins in the cytosol and inhibits the cellular apoptosis pathway (Junn et al., 2005; Karunakaran et al., 2007; Klawitter et al., 2013; Waak et al., 2009). The majority of the PD-linked DJ-1 mutations have lower affinity for ASK1 and Daxx compared to wild-type DJ-1 and tend to favour cell apoptosis. For instance, the P158del DJ-1 mutant affects the binding between DJ-1 and ASK1 and reduces DJ-1 anti-apoptotic potential, leading to apoptosis (Rannikko et al., 2013). In addition, the L166P DJ-1 PD-linked mutation, which is associated with increased apoptosis, cannot longer bind either ASK1 or Daxx (Im et al., 2010; Junn et al., 2005).

Different groups have shed some light on the molecular details of this mechanism. Under oxidizing conditions, it appears that nuclear DJ-1 retains a proportion of Daxx in the nucleus, preventing its exportation to the cytosol and its association with ASK1. In contrast, the nuclear fraction of L166P DJ-1 is not able to interact with Daxx to prevent ASK1-mediated apoptosis (Junn et al., 2005). Subsequently, an alternative mechanism exploited by DJ-1 to repress apoptosis has been postulated (Im et al., 2010). In that model, during oxidative stress, cytosolic DJ-1 prevents the dissociation of the complex between Trx1 (previously mentioned as part of the Nrf2 pathway) and ASK1, thus reducing the amount of ASK1 able to interact with activated Daxx in the cytosol and, in turn, inhibiting apoptosis. On the other hand, L166P DJ-1 mutant cannot prevent the dissociation of the complex ASK1/Trx1 upon oxidative stress, leaving most of ASK1 protein free to associate with cytosolic phosphorylated Daxx to initiate cell death. Interestingly, the M26I pathological mutation binds ASK1 with high affinity, even under non-oxidizing conditions (Waak et al., 2009). However, since M26I binds ASK1 in an aberrant site, it fails to abolish ASK1 activity in stressed cells. Furthermore, being that this pathological variant is mainly localized in the cytosol, even during oxidative stress, it cannot retain Daxx in the nucleus after a stress stimulus, thus inducing cell death (Waak et al., 2009).

As a further molecular mechanism, experiments carried out in *Drosophila* have shown that DJ-1 is a negative regulator of forkhead box O (FOXO) transcription factor, which in turn is responsible for *Daxx-Like Protein* gene expression, one of the key players of this apoptotic pathway (Hwang et al., 2013). In fact, flies knockout for *DJ-1β* gene, which is one of the two Drosophila *DJ-1* orthologous, have higher levels of Daxx-Like protein and are more vulnerable to oxidative stress compared to controls because of the lacking repressor function of DJ-1 (Hwang et al., 2013).

A further step toward the definition of DJ-1 activation stimuli has been made by Cao et al. (2014). They showed that different DJ-1 oxidation states "dictate" the cell response in the presence of ROS. The authors demonstrated that in cancer cells, a mild DJ-1 oxidation state is associated with the formation of the complex between DJ-1 and ASK1, thus inhibiting p38-related cell apoptosis and favouring c-Jun N-terminal protein kinase 1 (JNK1)-induced autophagy, to ensure cytoprotection. On the other hand, highly oxidized DJ-1 cannot retain ASK1 in the cytosol, which, in turn, stimulates cell death *via* p38 signalling. These results possibly suggest that DJ-1 acts as a stress sensor and can orchestrate cell response by triggering autophagy or apoptosis depending on the entity of the stimulus. Also, in the same paper, it has been reported that C106 is the key residue for DJ-1-dependent inhibition/activation of ASK1.

1.1.6. Glutathione and uncoupling proteins gene expression

DJ-1 overexpression has also been associated with increased levels of glutathione (GSH), the most abundant cellular thiol with antioxidant properties (Zhou and Freed, 2005). Furthermore, *DJ-1* deletion correlates with low mRNA levels of some uncoupling proteins in the *Substantia nigra pars compacta*, including UnCoupling Proteins 4 (UCP4) and 5 (UCP5), which are the main uncoupling factors expressed in the brain to prevent ROS accumulation (Guzman et al., 2010). Considering that the transcription pathways involved in GSH, UCP4 and UCP5 synthesis are still unresolved, a role for DJ-1 in stabilizing these gene transcripts can only be inferred based on the evidence that DJ-1 can bind RNA with nanomolar affinity (van der Brug et al., 2008).

In summary, DJ-1 has been shown to be involved in at least five different transcriptional pathways, but currently it is unclear whether all the above-mentioned signalling cascades are equally relevant across different brain regions and brain cells (*e.g.* neurons *versus* glial cells). In addition, the majority of data published about this topic have been obtained from cancer cells and, in particular, from non-neuronal cells, even when the effects of DJ-1 PD-linked mutations have been investigated. The p53 pathway has been studied in HEK-293, N2a and A549 cells (Fan et al., 2008; Ren et al., 2012), where p53 signalling is potentially deregulated, hindering the translation of these results in a more physiological context. The involvement of DJ-1 in the Nrf2 pathway is, by far, the most studied in the literature, but only few papers aimed to elucidate the molecular mechanisms in a neuronal context (Gan et al., 2010; Lev et al., 2015). It is important to note that the involvement of DJ-1 in the ERK/Elk signalling seems to be the most extensively investigated in the context of neurodegeneration and in a neuronal cell environment (Gao et al., 2012; Gu et al., 2009; Wang et al., 2011). Of note, mRNA levels of human ERK1 in the whole brain are almost twice as those measured in the majority of other tissues. Therefore, it is reasonable to hypothesize that this pathway might be relevant for PD. On the other hand, it has been shown that C106 is not essential for DJ-1 binding to ERK1/2 in murine neurons, suggesting that either DJ-1 does not operate as a sensor of oxidative stress in ERK1/2 signalling cascade or that there are additional layers of complexity in the mechanism underlying DJ-1 redox sensor activity in the brain that require further investigation (Gu et al., 2009).

2. Copper chaperone for SOD1

Besides the robust evidence supporting a role for DJ-1 as redox sensor (Cookson, 2012), more recent data highlight that DJ-1 may also exert cytoprotection against oxidative stress by acting as a copper chaperone for SOD1. SOD1 is one of the major cellular antioxidant defence systems against free radicals. It is mainly localized in the cytosol, but it is also found in the nucleus and in the mitochondrial intermembrane space (Fukai and Ushio-Fukai, 2011). Mutations in SOD1 represent a common cause of familial amyotrophic lateral sclerosis (Kaur et al., 2016). Of note, SOD1 may also play a role in PD: SOD1 transgenic mice are resistant to *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced neurotoxicity (Przedborski et al., 1992) and SOD1 overexpression enhances the survival of transplanted neurons in a rat model of PD (Nakao et al., 1995).

SOD1 activity is dependent on copper uptake, a process mediated by a specific protein called copper chaperone for superoxide dismutase (CCS) (Culotta et al., 1997). Interestingly, it has been shown that CCS knock-out mice retain 15–20% of SOD1 activity (Wong et al., 2000), suggesting the existence of alternative pathways able to activate SOD1. Xu and colleagues, using bimolecular fluorescence complementation assays, have shown that DJ-1 interacts with SOD1 (Xu et al., 2010). They have further demonstrated the ability of DJ-1 to stimulate SOD1 enzymatic activity in a copper dependent way (Xu et al., 2010), supporting the hypothesis that DJ-1 could be a suitable candidate for the CCS-independent SOD1 activation, under physiological and/or pathological conditions. Accordingly, experiments performed *in vitro* have demonstrated that DJ-1 binds different metals, including Hg(II), Cu(I) and Cu(II) (Bjorkblom et al., 2013; Girotto et al., 2014; Puno et al., 2013). The structural characterization of the copper-bound DJ-1 reveals the presence of two binding sites. The first one, which binds Cu(I), is located at the interface of two monomers and involves the two C53 residues that face each other. The second one binds Cu(II) and involves, among other residues, the C106 of each monomer (Girotto et al., 2014; Puno et al., 2013). Regarding C106, our group recently showed that four residues are within the copper coordination sphere: C106, E18, G75 and H126. While C106 and E18 are directly involved in metal coordination, G75 and H126 might be more important for the geometry of the binding (Girotto et al., 2014).

Even though the details of the transfer mechanism from DJ-1 to SOD1 are unknown, two different sets of experiments suggest that the copper binding site involving the C106 is the most likely responsible for the metal transfer. First, C53A mutant has been shown to be protective against oxidative-induced cell death (Canet-Aviles et al., 2004), suggesting that this copper-binding site does not play a major role in DJ-1 cytoprotective function. Second, the C53A DJ-1 mutant has been shown to retain its ability to activate SOD1 *in vitro* (Girotto et al., 2014). This opens a still unresolved issue on the nature of the oxidation state of copper. While C106 has been described to bind Cu(II), due to the reducing cytosolic environment, the physiological cellular transfer of copper from the lower to higher affinity sites should involve Cu(I). Even though this aspect needs further investigation, it is interesting to note that a small Cu(II)-complex named $Cu^{(II)}$ATSM has been shown to increase the proportion of fully metal loaded SOD1 in a mouse model of amyotrophic lateral sclerosis (Roberts et al., 2014). A similar molecular mechanism could involve the Cu(II)-DJ-1 complex. Of note, indirect evidence of the copper transfer from DJ-1 to SOD1 comes from a recent paper that showed that Cu $^{(II)}$ATSM treatment in human cardiac myocytes and in human coronary artery smooth muscle cells increases the interaction between DJ-1 and SOD1 and stimulates SOD1 activity (Srivastava et al., 2016). Whether and how DJ-1 binds Cu(II) in the cytosolic environment, in the absence of Cu $^{(II)}$ATSM, needs to be determined.

The possibility that DJ-1 acts as a copper chaperone for SOD1, in a CCS-independent manner, could explain, at least in part, the antioxidant properties associated to DJ-1, deserving future investigation. Since DJ-1 activity is oxidative-stress dependent, it is reasonable to speculate that DJ-1-dependent SOD1 maturation would occur under stress conditions. A possible alternative is that DJ-1 may act within the CCS-dependent pathway in assisting SOD1 maturation, meaning that the concomitant presence of both CCS and DJ-1 is important for SOD1 activation. Actually, in other cellular pathways involving copper transport and other metallo-chaperones, it has been proposed that a still unknown protein is responsible for the transfer of copper from glutathione to CCS (Banci et al., 2010).

In summary, DJ-1 may stimulate SOD1 by controlling the activation of redox-sensitive transcription pathways, as previously discussed, and by assisting the ligand-dependent maturation of SOD1. These two mechanisms are not mutually exclusive, especially considering the time required to reach the biological effect after an oxidative insult. Activation of gene expression has slower kinetics compared to SOD1 activation *via* metal loading. Thus, one stimulus could induce a rapid response, mediated by the ligand-dependent SOD1 maturation, while another may require a long-term response. As redundancy often occurs in biology, the presence of two pathways could be crucial to guarantee SOD1 functionality, even in case of failure of one of the two mechanisms.

3. Glycating stress and its importance in PD

In recent years, dicarbonyl stress has become a topic of great interest, being that unbalanced formation and elimination of α-oxoaldehyde metabolites are associated with different diseases, including

neurodegeneration (Rabbani and Thornalley, 2015). During glucose metabolism and lipid peroxidation several carbonyls are formed as by-products and exhibit high reactivity toward proteins, nucleic acids and lipids. Among them, methylglyoxal (MGO), which derives mainly from the catabolism of glyceraldehyde-3-phosphate and dihydroxyacetone phosphate, is one of the most reactive. MGO preferentially targets arginine and lysine residues, thus forming advanced glycation end-products (AGEs) (Kalapos, 1994; Lo et al., 1994; Rabbani and Thornalley, 2015), which cause protein aggregation and dysfunction (Adrover et al., 2014; Taghavi et al., 2016).

To counteract protein loss of function, cells have developed an efficient defence system against protein glycation, which mainly includes glyoxalase 1 and 2 enzymes. These proteins can directly react with MGO or glyoxal (GO) to form D-lactate or glycolate in two consecutive steps, using GSH as cofactor in the first step (Rabbani and Thornalley, 2015). Another protection from accumulation of AGEs is accomplished by deglycating enzymes, which can break off the glycation cascade by removing MGO or GO adducts from protein side-chains (Wu and Monnier, 2003). It is worth mentioning that glycating and oxidative stress are likely connected as robust experimental evidence exists showing that MGO causes a dramatic depletion of GSH and the formation of ROS, which in turn leads to oxidative stress (Di Loreto et al., 2004; Di Loreto et al., 2008; Kikuchi et al., 1999; Shangari and O'Brien, 2004). The importance of glycating stress in the context of neurodegeneration and, in particular, of PD has been recently reinvestigated, as the effects of protein glycation are more pronounced in the brain compared to other tissues. Moreover, it has been shown that neurons are much more vulnerable than astrocytes to glycating stress (Belanger et al., 2011). Specifically, both glyoxalase 1 and 2 are highly expressed in primary mouse astrocytes compared to neurons, with consequent higher enzymatic activity rates in astrocytes (9.9- and 2.5-fold, respectively). Accordingly, the presence of a highly efficient glyoxalase system in astrocytes was associated with a lower accumulation of AGEs compared with neurons, a 6-fold greater resistance to MGO toxicity, and a greater capacity to protect neurons against MGO in a co-culture system (Belanger et al., 2011). Moreover, strictly related to PD, data from a murine model based on a high glycemic index diet, indicate that inside the brain, neurons in the *substantia nigra* are among the most susceptible to this insult and the majority of MGO-modified proteins are localized in this cerebral area (Uchiki et al., 2012). A possible mechanism accounting for the hypersensitivity of these neurons to glycating stress is that MGO can react with dopamine as already showed in 1975 by Szent-Györgyi and McLaughlin (Szent-Gyorgyi and McLaughlin, 1975). It is now well known that glycated proteins can activate a specific receptor for AGEs (RAGE) and RAGE activation plays a central role in inducing inflammatory responses (Vicente Miranda and Outeiro, 2010). Therefore, if a protein produced in the brain is glycated and then secreted in the extracellular space, there is the possibility that it induces neuroinflammation *via* RAGE binding, thus favouring the onset and/or progression of neurodegeneration (Kierdorf and Fritz, 2013; Tobon-Velasco et al., 2014; Vicente Miranda and Outeiro, 2010).

4. DJ-1 glyoxalase activity

In an attempt to purify glyoxalase 1 from *E. coli*, a novel enzyme, named glyoxalase 3, able to catalyse the conversion of MGO directly into D-lactate without the need for exogenous GSH, has been characterized (Misra et al., 1995). In 2011, Subedi Ket al. demonstrated that the *E. coli* protein Hsp31, a homologue of DJ-1, belongs to the novel type of GSH-independent glyoxalases (Subedi et al., 2011). The catalytic site consists on a triad formed by E77, C185 and H186 residues, with the E77 and C185 residues conserved in eukaryotic DJ-1 orthologues (Subedi et al., 2011). Mutations in the cysteine and glutamic acid residues almost completely abolished glyoxalase activity, indicating that these residues are directly involved in the catalysis, while the histidine-mutated protein retains approximately 20% of residual activity (Subedi et al., 2011). Subsequently, fungal Hsp31 proteins from *Candida albicans* and *Saccharomyces cerevisiae* have also been shown to be GSH-independent glyoxalases (Bankapalli et al., 2015; Hasim et al., 2014; Wilson, 2014). The GSH-independent glyoxalase activity has been tested and observed in other DJ-1 orthologues and in human DJ-1 itself, even though the results are not as convincing as for Hsp31 (Bankapalli et al., 2015; Hasim et al., 2014; Kwon et al., 2013; Lee et al., 2016; Lee et al., 2012; Wilson, 2014). The putative glyoxalase activity of DJ-1 orthologues seems supported by structural data. Indeed, the predicted active site shows high homology through bacteria, *C. elegans* and mammals, even though the rest of the protein exhibits differences in the sequence (Lee et al., 2012). Specifically, while H186 of Hsp31 is not conserved in human DJ-1, H126 residue in the mammalian protein could replace its function in the active site, as suggested by Lee et al. (2012). On the other hand, it might be also possible that the lack of H186 conservation is responsible of the lower activity observed in the human DJ-1 compared to Hsp31. Considering that DJ-1 glyoxalase activity could directly modulate the levels of alpha-oxoaldehydes and being that oxidative and dicarbonyl stress seem to be connected, one possibility is that DJ-1 ability to reduce oxidative stress depends, at least in part, on its ability to eliminate MGO and GO. As previously discussed, neurons are particularly vulnerable to dicarbonyl stress (Di Loreto et al., 2004; Di Loreto et al., 2008; Kikuchi et al., 1999) and, in addition, there is increasing evidence showing that MGO and GO treatments in mammalian neurons and neuroblastoma cells lead to mitochondrial dysfunction (de Arriba et al., 2007; Tajes et al., 2014). Interestingly, DJ-1 deficiency has been associated with mitochondrial dysfunction in different cell types, including neurons (Guzman et al., 2010), and both D-lactate and glycolate were able to restore mitochondrial membrane potential in DJ-1 knock-down cells (Toyoda et al., 2014). This result seems to suggest that the products of glyoxalases can counteract MGO and GO effects on mitochondria and that mitochondrial dysfunction associated with DJ-1 knock-out might be related to a decrease of DJ-1 glyoxalase activity.

In spite of some emerging evidence, concerns remain about the effective physiological role of DJ-1 as a glyoxalase. For example, while Hsp31 has been described to have a higher activity toward MGO compared to DJ-1, the bacterial protein YajL, which is the closest orthologue of the mammalian DJ-1, does not show any enzymatic activity toward MGO (Lee et al., 2016). A recent paper argued that the glyoxalase activity of DJ-1 reflects its deglycase activity (Richarme et al., 2015). In addition, the calculated catalytic constant of DJ-1 (Lee et al., 2012) is three orders of magnitude lower than that of glyoxalase 1 (Ridderstrom et al., 1997), suggesting that DJ-1 might respond to intracellular changes of MGO levels only when the cellular concentration of GSH dramatically falls.

It is worth mentioning that, since *glyoxalase 1* promoter contains the ARE element, its gene expression is oxidative stress-dependent and is mediated by Nrf2 transcription factor. Therefore, it is possible that DJ-1 can also indirectly regulate glyoxalase 1 protein levels (Xue et al., 2012). Again, DJ-1 seems to operate at two levels within this process: it might promote the expression of glyoxalase 1 by activating the Nrf2-related pathway and it might act as glyoxalase enzyme, with the two activities likely to co-exist rather than being mutually exclusive.

5. DJ-1 deglycase activity

Together with its direct detoxification activity against MGO and GO, DJ-1 has also been described to possess a deglycase function that can remove MGO and GO from proteins and prevents Schiff bases from forming. In particular, hemithioacetal absorbance and reverse phase-HPLC analysis supported a role of DJ-1 as a deglycase protein in presence of glycated *N*-acetylcysteine, *N*-acetylarginine and *N*-acetylysine residues (Richarme et al., 2015). Accordingly, *in vitro* experiments of cysteines titration by 5,5′-dithiobis(nitrobenzoic acid) showed that DJ-1 deglycates bovine serum albumin, glyceraldehyde 3-phosphate

dehydrogenase, fructose-1,6-biphosphate, aldolase and aspartate transaminase, thus reducing the rate of Schiff base formation (Richarme et al., 2015). It is also noteworthy that YajL, YhbO and Hsp31 DJ-1 homologues have been reported to have deglycase activity *in vitro* (Abdallah et al., 2016; Mihoub et al., 2015). In addition, C106A mutant does not exhibit any enzymatic activity, suggesting that C106 is essential also for DJ-1 deglycase activity (Richarme et al., 2015). Very recently, Richarme and colleagues showed, *in vitro*, the ability of DJ-1 to prevent the formation of glycated guanine nucleotide, suggesting a role for the protein in the DNA repair system that contributes to maintaining genome integrity (Richarme et al., 2017). Since so far the deglycase activity has been described essentially by the same group, further validations with complementary experimental approaches and in alternative models are to be hoped. In fact, the role of DJ-1 as a *bona fide* deglycase protein and the relevance of this activity in the cell have not been proved at this time. For example, Pfaff and colleagues were unable to observe any deglycase activity, *in vitro*, using both human and *D. melanogaster* recombinant DJ-1 and that loss of *DJ-1β* did not correlate with increased AGE formation in flies (Pfaff et al., 2017). A possible reason for the lack of reproducibility of these results is the use of different protocols for protein purification, which may reflect the fraction of active purified DJ-1 (Pfaff et al., 2017; Richarme and Dairou, 2017). In addition, it is possible to predict that the net activity of DJ-1 as a putative deglycase depends on the availability of substrates and, therefore, on its subcellular localization. Protein glycation and redox levels are tissue-dependent and since DJ-1 is sensitive to oxidative stress, the effects of DJ-1 deglycase activity in different tissues might diverge. Another issue on the putative DJ-1 deglycase activity arises by considering the kinetic parameters of the reaction. DJ-1 is a rather inefficient deglycase which cannot compete with MGO-glycated protein formation and MGO removal by glyoxalase 1 (Lo et al., 1994). This raises the question of whether or not an enzyme that detoxifies the earliest glycation products with such a slow catalytic rate has physiological relevance in providing cell protection. In fact, these early adducts are in rapid equilibrium with free MGO and they are predicted to be efficiently detoxified by the highly active glyoxalase 1 and 2. Thus, DJ-1 activity might become relevant in the cell only in response to significant intracellular changes of MGO or GSH levels.

As summarized in Table 1, C106 seems to be essential for all the enzymatic activities associated with DJ-1 that have been reported in this review. In addition, also residue E18 appears to be essential in both copper coordination and glyoxalase activity, while the role of H126 is less established. Indeed, as described above, H126 is not directly involved in copper coordination being likely important for the geometry of the binding (Girotto et al., 2014). Moreover, H126 is not conserved in all DJ-1 homologues (Lee et al., 2012; Lin et al., 2012). In particular, the fact that *D. melanogaster* DJ-1β homologue, which is functionally very similar to human DJ-1, has a tyrosine residue in place of the histidine (Lin et al., 2012), suggests that H126 may serve a primary structural role in the protein, participating in the hydrogen bonds network. Even though there is evidence suggesting that H126 residue is not crucial for DJ-1 enzymatic activities, from a structural point of view it is worth mentioning that it forms a pocket on the protein surface together with E18 and C106 (Fig. 2). Altogether, these observations suggest that the described roles of DJ-1 are connected, although more investigations from independent laboratories are strictly required to prove these converging mechanisms.

Table 1
DJ-1 residues responsible for its purported physiological activities.

Residues	Function	References
C46, C53	Redox sensor	(Waak et al., 2009)
C106		(Aleyasin et al., 2007; Meulener et al., 2006; Takahashi-Niki et al., 2004)
E18, C106	Copper coordination	(Girotto et al., 2014)
G75, H126	Stabilisation of the geometry of copper binding site	(Girotto et al., 2014)
C106	Copper transfer to SOD1	(Girotto et al., 2014)
E18, C106, H126	Glyoxalase 3 activity	(Subedi et al., 2011)
C106A	Loss of function of both redox and neuroprotective functions	(Aleyasin et al., 2007; Waak et al., 2009)
C106S		(Takahashi-Niki et al., 2004)
C106A	Loss of function of deglycase activity	(Richarme et al., 2015)

6. Concluding remarks

Since the discovery of the involvement of DJ-1 in PD, a large effort has been made to understand the role of this protein in cells. In this review we focused on the most recent DJ-1 putative physiological roles and we discussed the idea that DJ-1 may exert its neuroprotection in different ways that can be correlated to each other (Fig. 3). It is now well accepted that DJ-1 possesses a direct antioxidant function and could serve as a sensor for oxidative stress inside cells. Accordingly, changes in the redox state of its sensitive cysteines are possibly the prime stimulus for the putative copper transfer to SOD1 and for the stimulation of deglycase/glyoxalase activity under stress conditions. In addition, DJ-1 could also act as an indirect antioxidant protein: under oxidizing conditions, it promotes the transcription of a subset of antioxidant genes, such as *SOD1*, *Trx1* and *NQO1*, to induce cell survival. It also serves as chaperone protein to prevent protein aggregation and ROS formation.

It is important to keep in mind that several enzymes participate in most of the cellular pathways described in this review, many of them with higher catalytic activity than DJ-1. In this regard, CCS accounts for approximately 80% of SOD1 maturation, while glyoxalase 1 and 2 constitute the system mainly involved in MGO detoxification. While DJ-1 appears to possess redundant functions, its role could become particularly important under stressful situations, such as in the presence of an altered cellular redox state. Based on the growing evidence that DJ-1 can perform multiple tasks in the cell, the protein could be included in the "moonlighting protein family". These proteins are defined as multifunctional polypeptides in which two or more physiologically relevant functions are performed by a single protein (Jeffery, 2014). The multimodal mechanism of action of DJ-1 in response to different sources of cellular stress could represent the mechanism through which DJ-1 exerts its neuronal cytoprotection against oxidative damage.

Unfortunately, our understanding of the activation mechanisms of DJ-1 neuroprotective function is limited and many questions still need to be answered, such as: what is the spatial specificity and temporal duration of the evoking stimulus? How is this process regulated in neurons? What are the global players involved in the response? It is unlikely that these patterns are activated in the same tissue, at the

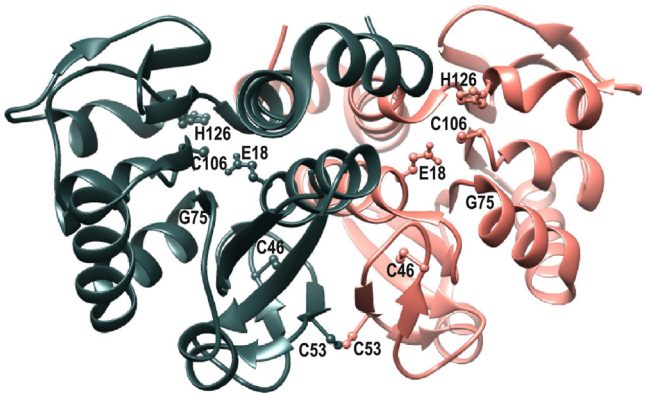

Fig. 2. Three-dimensional structure of DJ-1 in its dimeric form. The different monomers are represented with different colours and the residues involved in its purported physiological role have been emphasised. Residues E18 C106 and H126 form a pocket on DJ-1 protein surface.

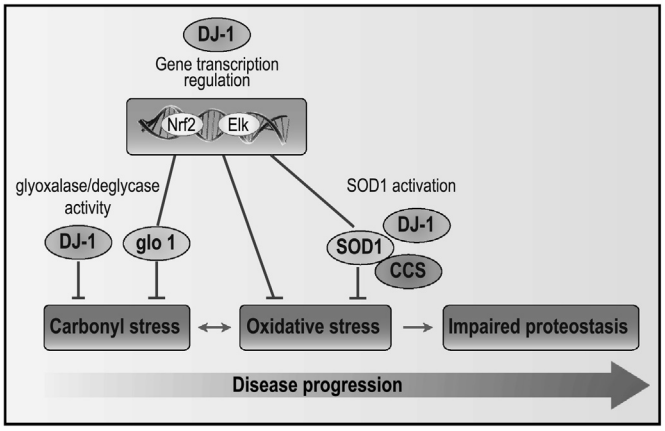

Fig. 3. Summary of the most recent physiological roles associated to DJ-1. DJ-1 has been described to regulate several transcription factors, to directly participate in SOD1 maturation and to possess a glyoxalase/deglycase activity. Interestingly these functions could be correlated.

same time and to the same extent, in response to a stimulus. For example, if a rapid cellular response against oxidative stress is required, cells would avoid the activation of gene expression as first line of defence, while in case of a long-term response, the stimulation of transcription pathways would be the primary cellular response. Furthermore, one signalling cascade could be more relevant than another in a specific tissue, making it difficult to predict which mechanisms are preferentially activated in specific situations. The future challenges in the field will be to better define DJ-1 antioxidant role in the context of neuronal survival with important implication for PD therapies.

Abbreviations

AGEs	advanced glycation end-products
ARE	antioxidant responsive element
ASK1	Apoptosis Signal-regulating Kinase 1
Bax	BCL2-Associated X protein
CCS	chaperone for superoxide dismutase
Daxx	death domain-associated protein 6
ERK/Elk	Extracellular Signal-regulated Kinase/ETS domain-containing protein
GO	glyoxal
GSH	glutathione
JNK1	c-Jun N-terminal protein kinase 1
MGO	methylglyoxal
NQO1	NAD(P)H quinone dehydrogenase 1
Nrf2	Nuclear factor E2-Related Factor 2
PD	Parkinson's disease
PTEN	Phosphatase and TENsin homologue deleted from chromosome 10
PI3K/PKB	PhosphoInositide 3-Kinase/Protein Kinase B
RAGE	receptor for AGEs
ROS	reactive oxygen species
SOD1	superoxide dismutase 1
TNF	Tumor Necrosis Factor
Trx1	thioredoxin 1

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

This work was supported by a grant from the Italian Ministry of Education, University and Research (2015T778JW). A.B. was supported by a postdoctoral fellowship from Università degli Studi di Padova (CPDR141155/14). We are grateful to Dr. Phillippa Carling for the English editing of the manuscript. We apologize to those whose work has not been cited.

References

Abdallah, J., et al., 2016. The DJ-1 superfamily members YhbO and YajL from *Escherichia coli* repair proteins from glycation by methylglyoxal and glyoxal. Biochem. Biophys. Res. Commun. 470, 282–286.
Adrover, M., et al., 2014. Mechanistic insights in glycation-induced protein aggregation. Biomacromolecules 15, 3449–3462.
Aleyasin, H., et al., 2007. The Parkinson's disease gene DJ-1 is also a key regulator of stroke-induced damage. Proc. Natl. Acad. Sci. U. S. A. 104, 18748–18753.
Ariga, H., et al., 2013. Neuroprotective function of DJ-1 in Parkinson's disease. Oxidative Med. Cell. Longev. 2013, 683920.
de Arriba, S.G., et al., 2007. Methylglyoxal impairs glucose metabolism and leads to energy depletion in neuronal cells—protection by carbonyl scavengers. Neurobiol. Aging 28, 1044–1050.
Ashcroft, M., et al., 2000. Stress signals utilize multiple pathways to stabilize p53. Mol. Cell. Biol. 20, 3224–3233.
Banci, L., et al., 2010. Affinity gradients drive copper to cellular destinations. Nature 465, 645–648.
Bankapalli, K., et al., 2015. Robust glyoxalase activity of Hsp31, a ThiJ/DJ-1/PfpI family member protein, is critical for oxidative stress resistance in *Saccharomyces cerevisiae*. J. Biol. Chem. 290, 26491–26507.
Batelli, S., et al., 2015. The Parkinson's disease-related protein DJ-1 protects dopaminergic neurons in vivo and cultured cells from alpha-synuclein and 6-hydroxydopamine toxicity. Neurodegener. Dis. 15, 13–23.
Belanger, M., et al., 2011. Role of the glyoxalase system in astrocyte-mediated neuroprotection. J. Neurosci. 31, 18338–18352.
Bjorkblom, B., et al., 2013. Parkinson disease protein DJ-1 binds metals and protects against metal-induced cytotoxicity. J. Biol. Chem. 288, 22809–22820.
Bonifati, V., et al., 2003. Mutations in the DJ-1 gene associated with autosomal recessive early-onset parkinsonism. Science 299, 256–259.
van der Brug, M.P., et al., 2008. RNA binding activity of the recessive parkinsonism protein DJ-1 supports involvement in multiple cellular pathways. Proc. Natl. Acad. Sci. U. S. A. 105, 10244–10249.
Canet-Aviles, R.M., et al., 2004. The Parkinson's disease protein DJ-1 is neuroprotective due to cysteine-sulfinic acid-driven mitochondrial localization. Proc. Natl. Acad. Sci. U. S. A. 101, 9103–9108.
Cao, J., et al., 2014. The oxidation states of DJ-1 dictate the cell fate in response to oxidative stress triggered by 4-hpr: autophagy or apoptosis? Antioxid. Redox Signal. 21, 1443–1459.
Clements, C.M., et al., 2006. DJ-1, a cancer- and Parkinson's disease-associated protein, stabilizes the antioxidant transcriptional master regulator Nrf2. Proc. Natl. Acad. Sci. U. S. A. 103, 15091–15096.
Cookson, M.R., 2010. DJ-1, PINK1, and their effects on mitochondrial pathways. Mov. Disord. 25 (Suppl. 1), S44–8.
Cookson, M.R., 2012. Parkinsonism due to mutations in PINK1, Parkin, and DJ-1 and oxidative stress and mitochondrial pathways. Cold Spring Harb. Perspect. Med. 2, a009415.
Culotta, V.C., et al., 1997. The copper chaperone for superoxide dismutase. J. Biol. Chem. 272, 23469–23472.
Di Loreto, S., et al., 2004. Methylglyoxal induces oxidative stress-dependent cell injury and up-regulation of interleukin-1beta and nerve growth factor in cultured hippocampal neuronal cells. Brain Res. 1006, 157–167.
Di Loreto, S., et al., 2008. Methylglyoxal causes strong weakening of detoxifying capacity and apoptotic cell death in rat hippocampal neurons. Int. J. Biochem. Cell Biol. 40, 245–257.
Erhardt, P., et al., 1999. B-Raf inhibits programmed cell death downstream of cytochrome c release from mitochondria by activating the MEK/Erk pathway. Mol. Cell. Biol. 19, 5308–5315.
Fan, J., et al., 2008. DJ-1 decreases Bax expression through repressing p53 transcriptional activity. J. Biol. Chem. 283, 4022–4030.
Fukai, T., Ushio-Fukai, M., 2011. Superoxide dismutases: role in redox signaling, vascular function, and diseases. Antioxid. Redox Signal. 15, 1583–1606.
Gan, L., et al., 2010. Keap1-Nrf2 activation in the presence and absence of DJ-1. Eur. J. Neurosci. 31, 967–977.
Gao, H., et al., 2012. DJ-1 protects dopaminergic neurons against rotenone-induced apoptosis by enhancing ERK-dependent mitophagy. J. Mol. Biol. 423, 232–248.
Girotto, S., et al., 2014. DJ-1 is a copper chaperone acting on SOD1 activation. J. Biol. Chem. 289, 10887–10899.
Gorrini, C., et al., 2013. Modulation of oxidative stress as an anticancer strategy. Nat. Rev. Drug Discov. 12, 931–947.
Gu, L., et al., 2009. Involvement of ERK1/2 signaling pathway in DJ-1-induced neuroprotection against oxidative stress. Biochem. Biophys. Res. Commun. 383, 469–474.
Guzman, J.N., et al., 2010. Oxidant stress evoked by pacemaking in dopaminergic neurons is attenuated by DJ-1. Nature 468, 696–700.

Hasim, S., et al., 2014. A glutathione-independent glyoxalase of the DJ-1 superfamily plays an important role in managing metabolically generated methylglyoxal in *Candida albicans*. J. Biol. Chem. 289, 1662–1674.
Hwang, S., et al., 2013. Drosophila DJ-1 decreases neural sensitivity to stress by negatively regulating Daxx-like protein through dFOXO. PLoS Genet. 9, e1003412.
Im, J.Y., et al., 2010. DJ-1 protects against oxidative damage by regulating the thioredoxin/ASK1 complex. Neurosci. Res. 67, 203–208.
Im, J.Y., et al., 2012. DJ-1 induces thioredoxin 1 expression through the Nrf2 pathway. Hum. Mol. Genet. 21, 3013–3024.
Jeffery, C.J., 2014. An introduction to protein moonlighting. Biochem. Soc. Trans. 42, 1679–1683.
Junn, E., et al., 2005. Interaction of DJ-1 with Daxx inhibits apoptosis signal-regulating kinase 1 activity and cell death. Proc. Natl. Acad. Sci. U. S. A. 102, 9691–9696.
Kalapos, M.P., 1994. Methylglyoxal toxicity in mammals. Toxicol. Lett. 73, 3–24.
Karunakaran, S., et al., 2007. Activation of apoptosis signal regulating kinase 1 (ASK1) and translocation of death-associated protein, Daxx, in substantia nigra pars compacta in a mouse model of Parkinson's disease: protection by alpha-lipoic acid. FASEB J. 21, 2226–2236.
Kato, I., et al., 2013. Oxidized DJ-1 inhibits p53 by sequestering p53 from promoters in a DNA-binding affinity-dependent manner. Mol. Cell. Biol. 33, 340–359.
Kaur, S.J., et al., 2016. Mutant SOD1 mediated pathogenesis of amyotrophic lateral sclerosis. Gene 577, 109–118.
Kierdorf, K., Fritz, G., 2013. RAGE regulation and signaling in inflammation and beyond. J. Leukoc. Biol. 94, 55–68.
Kikuchi, S., et al., 1999. Neurotoxicity of methylglyoxal and 3-deoxyglucosone on cultured cortical neurons: synergism between glycation and oxidative stress, possibly involved in neurodegenerative diseases. J. Neurosci. Res. 57, 280–289.
Kim, S.J., et al., 2002. ERK-1/2 and p38 kinase oppositely regulate nitric oxide-induced apoptosis of chondrocytes in association with p53, caspase-3, and differentiation status. J. Biol. Chem. 277, 1332–1339.
Kim, R.H., et al., 2005a. DJ-1, a novel regulator of the tumor suppressor PTEN. Cancer Cell 7, 263–273.
Kim, R.H., et al., 2005b. Hypersensitivity of DJ-1-deficient mice to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyrindine (MPTP) and oxidative stress. Proc. Natl. Acad. Sci. U. S. A. 102, 5215–5220.
Kim, Y.C., et al., 2009. Oxidation of DJ-1-dependent cell transformation through direct binding of DJ-1 to PTEN. Int. J. Oncol. 35, 1331–1341.
Kim, S.J., et al., 2012. Nuclear translocation of DJ-1 during oxidative stress-induced neuronal cell death. Free Radic. Biol. Med. 53, 936–950.
Kinumi, T., et al., 2004. Cysteine-106 of DJ-1 is the most sensitive cysteine residue to hydrogen peroxide-mediated oxidation in vivo in human umbilical vein endothelial cells. Biochem. Biophys. Res. Commun. 317, 722–728.
Klawitter, J., et al., 2013. Association of DJ-1/PTEN/AKT- and ASK1/p38-mediated cell signalling with ischaemic cardiomyopathy. Cardiovasc. Res. 97, 66–76.
Kumar, A., et al., 2011. Nuclear but not cytosolic phosphoinositide 3-kinase beta has an essential function in cell survival. Mol. Cell. Biol. 31, 2122–2133.
Kwon, K., et al., 2013. Novel glyoxalases from *Arabidopsis thaliana*. FEBS J. 280, 3328–3339.
Lee, J.Y., et al., 2012. Human DJ-1 and its homologs are novel glyoxalases. Hum. Mol. Genet. 21, 3215–3225.
Lee, C., et al., 2016. Characterization of the *Escherichia coli* YajL, YhbO and ElbB glyoxalases. FEMS Microbiol. Lett. 363.
Lev, N., et al., 2015. A DJ-1 based peptide attenuates dopaminergic degeneration in mice models of Parkinson's disease via enhancing Nrf2. PLoS One 10, e0127549.
Lin, J., et al., 2012. Conservation of oxidative protein stabilization in an insect homologue of parkinsonism-associated protein DJ-1. Biochemistry 51, 3799–3807.
Liu, D.H., et al., 2013. Endogenous nitric oxide induces activation of apoptosis signal-regulating kinase 1 via S-nitrosylation in rat hippocampus during cerebral ischemia-reperfusion. Neuroscience 229, 36–48.
Lo, T.W., et al., 1994. Binding and modification of proteins by methylglyoxal under physiological conditions. A kinetic and mechanistic study with N alpha-acetylarginine, N alpha-acetylcysteine, and N alpha-acetyllysine, and bovine serum albumin. J. Biol. Chem. 269, 32299–32305.
Meulener, M., et al., 2005. Drosophila DJ-1 mutants are selectively sensitive to environmental toxins associated with Parkinson's disease. Curr. Biol. 15, 1572–1577.
Meulener, M.C., et al., 2006. Mutational analysis of DJ-1 in *Drosophila* implicates functional inactivation by oxidative damage and aging. Proc. Natl. Acad. Sci. U. S. A. 103, 12517–12522.
Mihoub, M., et al., 2015. The DJ-1 superfamily member Hsp31 repairs proteins from glycation by methylglyoxal and glyoxal. Biochem. Biophys. Res. Commun. 463, 1305–1310.
Misra, K., et al., 1995. Glyoxalase III from *Escherichia coli*: a single novel enzyme for the conversion of methylglyoxal into D-lactate without reduced glutathione. Biochem. J. 305 (Pt 3), 999–1003.
Nakao, N., et al., 1995. Overexpressing Cu/Zn superoxide dismutase enhances survival of transplanted neurons in a rat model of Parkinson's disease. Nat. Med. 1, 226–231.
Ottolini, D., et al., 2013. The Parkinson disease-related protein DJ-1 counteracts mitochondrial impairment induced by the tumour suppressor protein p53 by enhancing endoplasmic reticulum-mitochondria tethering. Hum. Mol. Genet. 22, 2152–2168.
Pfaff, D.H., et al., 2017. Evidence against a role for the parkinsonism-associated protein DJ-1 in methylglyoxal detoxification. J. Biol. Chem. 292, 685–690.
Przedborski, S., et al., 1992. Transgenic mice with increased Cu/Zn-superoxide dismutase activity are resistant to N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced neurotoxicity. J. Neurosci. 12, 1658–1667.
Puno, M.R., et al., 2013. Structure of Cu(I)-bound DJ-1 reveals a biscysteinate metal binding site at the homodimer interface: insights into mutational inactivation of DJ-1 in Parkinsonism. J. Am. Chem. Soc. 135, 15974–15977.
Rabbani, N., Thornalley, P.J., 2015. Dicarbonyl stress in cell and tissue dysfunction contributing to ageing and disease. Biochem. Biophys. Res. Commun. 458, 221–226.
Rannikko, E.H., et al., 2013. Loss of DJ-1 protein stability and cytoprotective function by Parkinson's disease-associated proline-158 deletion. J. Neurochem. 125, 314–327.
Ren, H., et al., 2012. L166P mutant DJ-1 promotes cell death by dissociating Bax from mitochondrial Bcl-XL. Mol. Neurodegener. 7, 40.
Richarme, G., Dairou, J., 2017. Parkinsonism-associated protein DJ-1 is a bona fide deglycase. Biochem. Biophys. Res. Commun. 483, 387–391.
Richarme, G., et al., 2015. Parkinsonism-associated protein DJ-1/Park7 is a major protein deglycase that repairs methylglyoxal- and glyoxal-glycated cysteine, arginine, and lysine residues. J. Biol. Chem. 290, 1885–1897.
Richarme, G., et al., 2017. Guanine glycation repair by DJ-1/Park7 and its bacterial homologs. Science.
Ridderstrom, M., et al., 1997. Mutagenesis of residue 157 in the active site of human glyoxalase I. Biochem. J. 328 (Pt 1), 231–235.
Roberts, B.R., et al., 2014. Oral treatment with Cu(II)(atsm) increases mutant SOD1 in vivo but protects motor neurons and improves the phenotype of a transgenic mouse model of amyotrophic lateral sclerosis. J. Neurosci. 34, 8021–8031.
Salmena, L., et al., 2008. Tenets of PTEN tumor suppression. Cell 133, 403–414.
Shangari, N., O'Brien, P.J., 2004. The cytotoxic mechanism of glyoxal involves oxidative stress. Biochem. Pharmacol. 68, 1433–1442.
Srivastava, S., et al., 2016. Cardioprotective effects of Cu(II)ATSM in human vascular smooth muscle cells and cardiomyocytes mediated by Nrf2 and DJ-1. Sci Rep 6, 7.
Subedi, K.P., et al., 2011. Hsp31 of *Escherichia coli* K-12 is glyoxalase III. Mol. Microbiol. 81, 926–936.
Szent-Gyorgyi, A., McLaughlin, J.A., 1975. Interaction of glyoxal and methylglyoxal with biogenic amines. Proc. Natl. Acad. Sci. U. S. A. 72, 1610–1611.
Taghavi, F., et al., 2016. The status of glycation in protein aggregation. Int. J. Biol. Macromol.
Taira, T., et al., 2004. DJ-1 has a role in antioxidative stress to prevent cell death. EMBO Rep. 5, 213–218.
Tajes, M., et al., 2014. Methylglyoxal reduces mitochondrial potential and activates Bax and caspase-3 in neurons: implications for Alzheimer's disease. Neurosci. Lett. 580, 78–82.
Takahashi-Niki, K., et al., 2004. Reduced anti-oxidative stress activities of DJ-1 mutants found in Parkinson's disease patients. Biochem. Biophys. Res. Commun. 230, 389–397.
Thomas, K.J., et al., 2011. DJ-1 acts in parallel to the PINK1/parkin pathway to control mitochondrial function and autophagy. Hum. Mol. Genet. 20, 40–50.
Tobon-Velasco, J.C., et al., 2014. Receptor for AGEs (RAGE) as mediator of NF-kB pathway activation in neuroinflammation and oxidative stress. CNS Neurol. Disord. Drug Targets 13, 1615–1626.
Toyoda, Y., et al., 2014. Products of the Parkinson's disease-related glyoxalase DJ-1, D-lactate and glycolate, support mitochondrial membrane potential and neuronal survival. Biol. Open 3, 777–784.
Tran, S.E., et al., 2001. MAPK/ERK overrides the apoptotic signaling from Fas, TNF, and TRAIL receptors. J. Biol. Chem. 276, 16484–16490.
Uchiki, T., et al., 2012. Glycation-altered proteolysis as a pathobiologic mechanism that links dietary glycemic index, aging, and age-related disease (in nondiabetics). Aging Cell 11, 1–13.
Vicente Miranda, H., Outeiro, T.F., 2010. The sour side of neurodegenerative disorders: the effects of protein glycation. J. Pathol. 221, 13–25.
Waak, J., et al., 2009. Oxidizable residues mediating protein stability and cytoprotective interaction of DJ-1 with apoptosis signal-regulating kinase 1. J. Biol. Chem. 284, 14245–14257.
Wang, Z., et al., 2011. DJ-1 modulates the expression of Cu/Zn-superoxide dismutase-1 through the Erk1/2-Elk1 pathway in neuroprotection. Ann. Neurol. 70, 591–599.
Wilson, M.A., 2014. Metabolic role for yeast DJ-1 superfamily proteins. Proc. Natl. Acad. Sci. U. S. A. 111, 6858–6859.
Wilson, M.A., et al., 2003. The 1.1-A resolution crystal structure of DJ-1, the protein mutated in autosomal recessive early onset Parkinson's disease. Proc. Natl. Acad. Sci. U. S. A. 100, 9256–9261.
Wong, P.C., et al., 2000. Copper chaperone for superoxide dismutase is essential to activate mammalian Cu/Zn superoxide dismutase. Proc. Natl. Acad. Sci. U. S. A. 97, 2886–2891.
Wu, X., Monnier, V.M., 2003. Enzymatic deglycation of proteins. Arch. Biochem. Biophys. 419, 16–24.
Xu, X.M., et al., 2010. The Arabidopsis DJ-1a protein confers stress protection through cytosolic SOD activation. J. Cell Sci. 123, 1644–1651.
Xue, M., et al., 2012. Transcriptional control of glyoxalase 1 by Nrf2 provides a stress-responsive defence against dicarbonyl glycation. Biochem. J. 443, 213–222.
Yamaguchi, S., et al., 2012. Transcriptional activation of low-density lipoprotein receptor gene by DJ-1 and effect of DJ-1 on cholesterol homeostasis. PLoS One 7, e38144.
Yan, Y.F., et al., 2015. DJ-1 upregulates anti-oxidant enzymes and attenuates hypoxia/reoxygenation-induced oxidative stress by activation of the nuclear factor erythroid 2-like 2 signaling pathway. Mol. Med. Rep. 12, 4734–4742.
Zhou, W., Freed, C.R., 2005. DJ-1 up-regulates glutathione synthesis during oxidative stress and inhibits A53T alpha-synuclein toxicity. J. Biol. Chem. 280, 43150–43158.