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Review

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

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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

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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

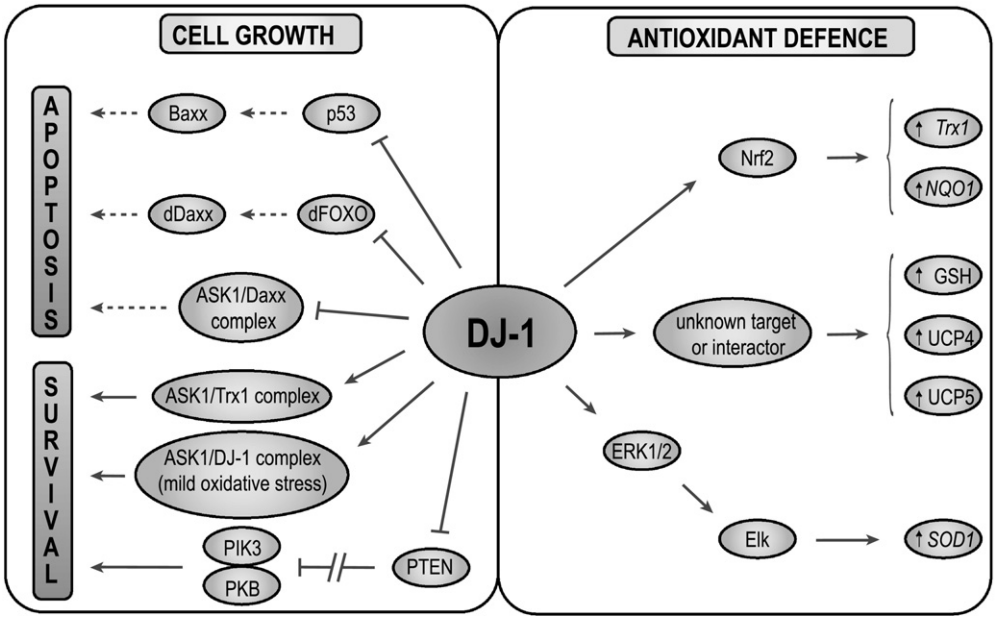

Fig. 1. Summary of the gene expression pathways regulated by DJ-1. These pathways are involved in antioxidant defence or in cell survival. See text for details.