



● INVITED REVIEW

The role of DJ-1 in the oxidative stress cell death cascade after stroke

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Abstract

Oxidative stress is closely associated with secondary cell death in many disorders of the central nervous system including stroke, Parkinson's disease, Alzheimer's disease. Among many aberrant oxidative stress-associated proteins, DJ-1 has been associated with the oxidative stress cell death cascade primarily in Parkinson's disease. Although principally expressed in the cytoplasm and nucleus, DJ-1 can be secreted into the serum under pathological condition. Recently, a close pathological association between DJ-1 and oxidative stress in stroke has been implicated. To this end, we and others have demonstrated the important role of mitochondria in neuroprotection for stroke by demonstrating that the translocation of DJ-1 in the mitochondria could potentially mitigate mitochondrial injury. Here, we discuss our recent findings testing the hypothesis that DJ-1 not only functions as a form of intracellular protection from oxidative stress, but that it also utilizes paracrine and/or autocrine cues in order to accomplish extracellular signaling between neighboring neuronal cells, resulting in neuroprotection. This article highlights recent evidence supporting the status of DJ-1 as key anti-oxidative stress therapeutic target for stroke.

Key Words: cerebral ischemia; neuroprotection; mitochondria; translocation; extracellular signaling

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Targeting oxidative stress pathway for arresting stroke secondary cell death

Despite significant scientific progress in the understanding and treatment of stroke, developing new and effective therapies to combat the disease continues to be a primary clinical concern. Neural tissue damage caused by stroke is attributable to a disruption in blood flow to the brain, resulting in a lack of glucose, oxygen, and other nutrients. This in turn results in an infarcted core, which quickly becomes necrotic and the formation of an ischemic penumbra. This penumbra has been shown to be receptive to therapeutic interventions during the sub-acute period (Heiss, 2000; Warach, 2003; Lo, 2008). As time progresses, the penumbra assimilates to become part of the necrotic core *via* various mechanisms of secondary cell death. Among the many neurodegenerative pathways, oxidative stress has been proven to aggravate the process of secondary cell death in the central nervous system not only in stroke, but in Parkinson's disease (PD) and Alzheimer's disease as well (Dawson and Dawson, 2003; Nakamura and Lipton, 2010). DJ-1 is a multifunctional redox-sensitive protein that has been associated with the oxidative stress cell death cascade. DJ-1 provides neuroprotection from this form of cell death in multiple pathways, but most importantly by reducing mitochondrial oxidative

stress (Canet-Avilés et al., 2004), molecular chaperoning of PD-aggregating protein α -synuclein (Dawson and Dawson, 2003), stimulating anti-apoptotic and antioxidative gene expression (Clements et al., 2006; Fan et al., 2008), promoting the pro-survival Akt pathway while impeding the apoptosis signal-regulating kinase pathway (Junn et al., 2005; Yang et al., 2005; Gerner et al., 2007), and by acting as a positive regulator of androgen receptor-dependent transcription (Takahashi et al., 2001; Dawson and Dawson, 2003; Niki et al., 2003; Tillman et al., 2007). Typically found in the cytoplasm and nucleus, DJ-1 can be secreted into the serum in the presence of pathology, such as melanoma or breast cancer (Tsuboi et al., 2008; Waak et al., 2009), and can also be translocated into the mitochondria of various mammalian cells by mitogen stimulation or, of particular interest, oxidative stress (Canet-Avilés et al., 2004; Tsuboi et al., 2008; Junn et al., 2009). As an additional testament to the close association between DJ-1 and oxidative stress following stroke, as well as the importance of mitochondria in preventing free radical generation, this migration to the mitochondria has been linked to a decrease in aberrant formation of free radicals such as mitochondrial reactive oxygen species (Canet-Avilés et al., 2004; Nakamura and Lipton, 2010). Here, we discuss our recent findings that DJ-1 not only functions as a form of intracellular protection from oxidative stress, but that it also

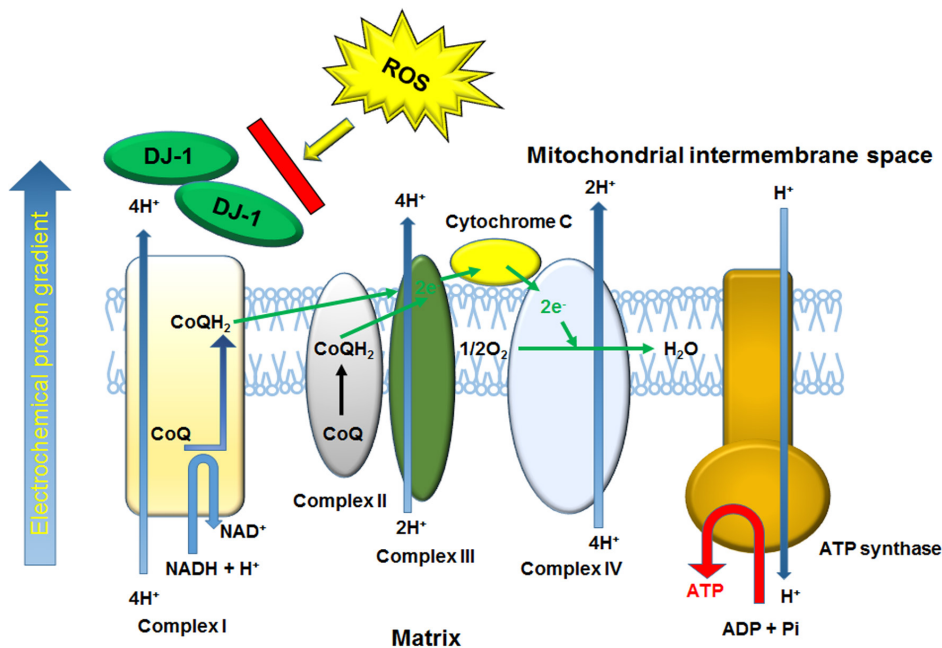


Figure 1 Summarized DJ-1 function for protecting mitochondrial function.

Under ischemic condition, cytoplasmic DJ-1 translocated into the mitochondrial inter membrane where the electron transport chain enzymes (complex I–IV and ATP synthase) generate ATP, and protected mitochondria complex I against ROS such as superoxide. DJ-1 dysfunction not only induces the cytochrome c-mediated apoptosis signaling pathway (Osman et al., 2011) but also damages mitochondrial DNA, leading to neurodegenerative diseases (cf. PD). CoQ: Ubiquinone (oxidized form). CoQH₂: ubiquinol (reduced form).

utilizes paracrine and/or autocrine cues in order to accomplish extracellular signaling between neighboring neuronal cells, resulting in neuroprotection (Kaneko et al., 2014a, b). Our commitment to the advancement of cell therapy from the laboratory to the clinical setting led us to the use of human neural progenitor cells (hNPCs) as a medium to determine whether DJ-1 translocated into the mitochondria and secreted under hypoxic-ischemic conditions (Kaneko et al., 2014a). We confirmed the hypothesis that DJ-1 translocated into the mitochondria with subsequent DJ-1 protein secretion into the serum, using cultured primary rat neural cells (PRNCs; ratio of astrocytes/neurons is 6/4) exposed to an experimental stroke condition (Kaneko et al., 2014b).

DJ-1: key anti-oxidative stress therapeutic target for stroke

In our papers (Kaneko et al., 2014a, b), we showed that under oxygen glucose deprivation (OGD), an established experimental model of stroke, DJ-1 had translocated into the healthy mitochondria, and DJ-1 protein was secreted by the injured hNPCs and PRNCs. Capturing of extracellular DJ-1 by using anti-DJ-1 antibody had reduced both cell viability and mitochondrial activity, whereas intracellular glutathione (GSH) levels, a marker of oxidative stress, significantly increased. Interestingly, OGD also reversed the ratio of astrocyte-to-neuron cells, from a ratio of 6:4 to 4:6, indicating that astrocytes rescue neurons by unknown mechanisms. Our findings revealed that DJ-1 plays an active role in the early phase of experimental stroke by integrating the mitochondrial pathway: DJ-1 expression was immediately increased after the injury and had efficiently translocated into the mitochondria in both hNPCs and PRNCs.

Next, we focused on oxidative damage, a major secondary cell death pathway subsequent to the OGD-reperfusion phase (Pompella et al., 2003; Shelly, 2009). We measured GSH production, which may render neuroprotective effects against reactive oxygen species (ROS) and may also modulate cell proliferation. Compared to normoxic conditions, the increase in GSH production in hNPCs after 2-hour reperfu-

sion following OGD was approximately two-fold. This indicates that an endogenous repair mechanism was activated to protect the hNPCs from oxidative damage, by facilitating an increase in intracellular GSH levels in response to cell death injury. This supports previous findings and implicates that secreted type DJ-1 exerts neuroprotective effects in stem/progenitor cells (Mullett et al., 2008; Gao et al., 2012).

After OGD exposure, cell viability and mitochondrial activity were significantly decreased. In contrast, GSH levels were increased, compared with normoxic conditions. Physiologically, the loss of DJ-1 perturbs the endogenous and protective actions of PRNCs against oxidative stress (Martinat et al., 2004; Miyazaki et al., 2008).

Localization of DJ-1 in the PRNCs was viewed under immunofluorescent microscopy. Of interest, the results revealed translocation of DJ-1 into the mitochondrial inner membrane following the hypoxic-ischemic insult (**Figure 1**). This illustrates that DJ-1 serves as a sensitive biomarker of early protection against neurodegeneration, in response to acute hypoxic-ischemic injury, and may be detected both secreted type DJ-1 and intercellular type DJ-1 (Martinat et al., 2004; Yanagisawa et al., 2008).

In cultured PRNCs subjected to normoxic and hypoxic-ischemic conditions, we counted the number of MAP2-positive neuronal cells and extrapolated the number of astrocytes. Our analysis revealed that the hypoxia-ischemia had significantly reversed the ratio of astrocytes to neurons (6:4) when compared with normoxic conditions (4:6) ($P < 0.01$). Additionally, DJ-1 selectively translocated into healthy (polarized) mitochondria comparison with damaged (depolarized) mitochondria, although it is unclear that hypoxic-ischemic condition affects the DJ-1 dynamics. Our experiments demonstrate that DJ-1 is involved with the preservation of functional mitochondria; DJ-1 co-localized with active mitochondria, but not with inactive mitochondria.

Perspective: advancing DJ-1 for stroke therapeutics

Our recent reports provided insights into the molecular

mechanism of DJ-1 for its role in neuroprotection against stroke model. We showed a novel neuroprotective event involving DJ-1 translocation into the mitochondria following hypoxemia in both hNPCs and PRNCs. We found similar outcomes implicating DJ-1 mitochondrial translocation while using either hNPCs or PRNCs; therefore, based on our studies, we can deduce that DJ-1 has a direct action on stem/progenitor cells. Our results indicate that under hypoxic conditions, DJ-1 favors neuronal rescue, as there is an observed reversal of the astrocyte to neuron rescue ratio (6:4 to 4:6). This discovery opens new opportunities for the development of therapeutics aimed at protecting against mitochondrial deficits, including stroke and other neurological disorders. An alternative possibility is that astrocytes are more vulnerable against ROS/lipid peroxides, and this warrants further investigation. Our results also revealed that DJ-1 is secreted from neuronal cells, DJ-1 is sequestered. Decreased levels of DJ-1 correspond to a decline in mitochondrial activity, and ultimately to decreased cell viability under ischemic, or OGD conditions. This observation demonstrates that DJ-1 must undergo mitochondrial translocation following extracellular secretion under ischemic conditions, thus revealing the neuroprotective role DJ-1 has during states of hypoxia, such as in stroke.

A key function of DJ-1 is in maintaining the activity of mitochondrial complex I under oxidative stress (Figure 1) (Hayashi et al., 2009; Kahle et al., 2009; Ircher et al., 2010). Following ischemic neuronal cell death, mitochondrial complex I automatically releases ROS, which subsequently acts upon the neighboring environment, inducing additional mitochondria to generate ROS *via* permeability transition pore opening, in an attempt to halt progression of secondary cell death. The mitochondrial complex I tightly regulates ATP production in eukaryotic cells; dysfunction of the complexes induces cell death (Taira et al., 2004; Foti et al., 2010). Translocation of DJ-1 into the mitochondria sequesters ROS-induced toxicity endogenously. Analogous findings have been observed in cases of breast cancer and melanoma, where DJ-1 is released under hypoxic conditions into the serum *in vitro* and *in vivo* (Le Naour et al., 2001; Miura et al., 2002; Kim et al., 2010). The translocation of DJ-1 into the mitochondria may turn the course of cellular activity toward pro-survival mechanisms, including mitochondrial movement and increased cell-to-cell interaction. In addition, DJ-1 may also act through multi-pronged neuroprotective processes, as evidenced through the varied results received on MTT and cell survival following sequestration of DJ-1.

To date, there have been a number of potential therapeutic molecules that undergo nuclear translocation, and thereafter exerting neuroprotection in stroke (Yang et al., 2008, 2009; Gan et al., 2010; Pallast et al., 2010). Hence, our DJ-1 studies support the postulation that DJ-1 plays a key role in maintaining functioning mitochondria and a dynamic cell structure (Figure 1), thus maintaining a balance between fission and fusion. Our present findings are complemented by recent literature that links DJ-1 to inflammatory pathways and oxidative stress (Aleyasin et al., 2007; Yanagisawa et al., 2008; Mullett et al., 2009). Although at the time of ischemic injury we found increased levels of the antioxidant GSH

that correspond to mitochondrial translocation of DJ-1, sequestration of extracellular DJ-1 with antibody resulted in increased GSH levels, but decreased mitochondrial activity and therefore cell viability. Use of stem/progenitor cells, in this case specifically PRNCs, allowed us to represent both cell types. These findings implicate that although GSH plays an important role in neuroprotection during stroke, its effects are inconsequential in the presence of DJ-1 deficit.

The mitochondria stands as a viable therapeutic target for the treatment of stroke as evidenced through various pathways. Indeed, altered expression of the primary inhibitor of tissue-type plasminogen activators, plasminogen activator inhibitor-1, promotes apoptotic sequence involving cytochrome c release from the mitochondria (Soeda et al., 2008). Moreover, the small amino acid N-acetylaspartate, synthesized by neuronal mitochondria, is released into serum following reperfusion in animal models of brain ischemia and in serum of patients following acute ischemic stroke (Elting et al., 2004). Additionally, DJ-1 promotes angiogenesis and osteogenesis by way of activating fibroblast growth factor receptor-1 signaling (Kim et al., 2012).

In consideration of our recent findings, specifically that DJ-1 extracellular secretion and mitochondrial translocation occur in cultured hNPCs and PRNCs, it is plausible that an *in vivo* model may mimic the effects of DJ-1 in the stem progenitor cell-populated neurogenic sites of lateral ventricle and hippocampal dentate gyrus. In concert with other studies (Görner et al., 2007; Vasseur et al., 2009; Aron et al., 2010; Yan and Pu, 2010), we advance the concept that DJ-1 is a protein essential for the maintenance of stem/progenitor cell survival in response to ischemia, which presents a unique strategy for treating stroke.

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