

● PERSPECTIVE

DJ-1 as a deglycating enzyme: a unique function to explain a multifaceted protein?

The Parkinson's disease (PD)-associated protein DJ-1 is considered a multifunctional protein involved in oxidative stress responses. Although a large variety of functions has been attributed to DJ-1, currently no consensus has been found on its effective cellular activity. Indeed, the protein has been described as a transcriptional modulator, a regulator of mitochondrial activity, a stabilizer of the nuclear factor erythroid 2-related factor (Nrf2), a chaperone, a protease, and a glutathione (GSH)-independent glyoxalase (Ariga et al., 2013). Very recently, the additional participation of the protein to carbonyl stress defense has been emerging (Richarme et al., 2015). Carbonyl stress is a harmful condition characterized by an excessive amount of reactive carbonyl species with glycation potential. These compounds are unavoidable intermediates of metabolic pathways and are characterized by a high level of reactivity towards nucleophilic molecules. Carbonyl attack principally involves biomolecules such as proteins, nucleic acids, and phospholipids, causing cytotoxicity and genotoxicity. Although glucose is the most abundant glycation agent, methylglyoxal (MGO) and glyoxal (GO) are considered the principal glycation players because of their high reactivity. These species, generated as by-products of the glycolytic flux, are capable of reacting with biological molecules affecting their stability and functions. In particular, these compounds can react with arginine and lysine residues of proteins and with guanosine and deoxyguanosine nucleotides (Thornalley, 2008). Spontaneous glycation promotes the reversible formation of an unstable Schiff base that undergoes a rearrangement into a more stable ketoamine, named Amadori product. This molecule can further rearrange to eventually yield irreversible advanced glycation end products (AGEs), which have been associated with diabetes and several age-related diseases (Thornalley, 2008). To counteract these dangerous modifications, cells have developed different protective mechanisms, which include aldoketoreductases that convert carbonyls into alcohols, glyoxalases that degrade methylglyoxal and glyoxal releasing lactate and glycolate, respectively, and fructosamine-3-kinases that phosphorylates lysine-fructosamines generated after glucose glycation (Richarme et al., 2015). In this regard, the activity of DJ-1 as a deglycating enzyme recently reported by Richarme and co-workers is of particular interest. The investigators have shown, *in vitro*, that DJ-1 is able to restore damaged proteins, preventing Schiff base formation. Specifically, DJ-1 has been demonstrated to restore glycated N-acetylcysteine, N-acetylarginine and N-acetyllysine amino acids after their reaction with MGO. Moreover, this function has been confirmed using different glycated proteins, including bovine serum albumin, glyceraldehyde 3-phosphate dehydrogenase, aldolase, fructose-1,6-biphosphate, and aspartate transaminase. Interestingly, this activity seems to be dependent on a highly-conserved cysteine residue located at position 106, whose mutation has been shown to impair DJ-1-dependent deglycation. Noteworthy, this function seems to be exerted during early glycation events, before AGEs formation. Indeed, using bovine serum albumin as glycation target, the authors have shown that, once the Schiff base is formed, DJ-1 cannot deglycate it, while it acts on aminocarbonyl, the Schiff base precursor (Richarme et al., 2015). Besides acting on glycated proteins, the same group has reported, very recently, that DJ-1 is able to prevent nucleic acids glycation by performing the so-called "nucleotide sanitization" (Richarme et al., 2017). Similarly to the protein related process, DJ-1 has been described to work only on early steps of the glycation reaction. Moreover, the C106S DJ-1 mutant does not present deglycating activity, further confirming that this residue is required for its protective function against carbonyl stress.

As emphasized by Richarme and colleagues, this new function could reconcile some of the previously described activities attributed to DJ-1 (Richarme et al., 2015). Indeed, to perform its deglycase activity, DJ-1 acts as: (i) a chaperone to interact with glycated molecules; (ii) a glyoxalase 1 to transform hemithioacetals into thioesters and aminocarbonyls into amides; (iii) a glyoxalase 2 to cut thioesters for cysteine deglycation; and (iv) a protease to break amide bonds favoring lysine/arginine deglycation (Richarme et al., 2015). Moreover, this function may contribute to justify the multifarious subcellular localization described for DJ-1. Indeed, the protein is mainly cytosolic but it has been also detected at the nuclear and mitochondrial level (Ariga et al., 2013). These subcellular localizations may reflect the different compartments in which the protein exerts its deglycating function, acting on both proteins and nucleic acids. Very interestingly, the deglycating activity attributed to DJ-1 might also explain the participation of the protein in tumor growth. Experimental evidence supports the overexpression of DJ-1 in many tumor types, such as prostate cancer, ovarian carcinoma, breast cancer, and acute leukemia (Cao et al., 2015). Indeed, DJ-1 has been shown to stimulate cell proliferation and to repress apoptosis, two key events that are often dysregulated in tumors (Cao et al., 2015). For example, DJ-1 has been suggested to favor survival by stimulating the protein kinase B (PKB/Akt) pathway and inhibiting its repressor, the phosphatase and tensin homolog deleted on chromosome 10 (PTEN), a known tumor suppressor (Cao et al., 2015). In this contest, the emerging role of DJ-1 as a novel deglycase may represent a different mechanism through which the protein could promote tumor growth. Actually, malignant tumors are characterized by high levels of glycolysis, the so-called "Warburg Effect", and the enhanced glycolytic flux could make DNA, proteins and lipids more susceptible to glycation than normal cells. Nonetheless, since DJ-1 is highly expressed in tumor cells too, its function as a deglycase could represent a mechanism to preserve malignant cells integrity, thus favoring their sustained proliferation.

Another aspect that could be explained by the new activity associated with DJ-1 is the recently described connection between diabetes and PD. If on one hand diabetes represents a risk factor for PD development (Yang et al., 2017), on the other hand, more than 60% of the PD patients present an impairment in the insulin signaling and are glucose intolerant (Santiago and Potashkin, 2013). In this frame, the recent involvement of DJ-1 in diabetes is worthy of note. Indeed, Jain and colleagues have found that DJ-1 is down-regulated in pancreatic islets of type II diabetes mellitus patients, while in non-diabetic individuals, its expression increases with aging (Jain et al., 2012). Furthermore, the investigators reported that DJ-1-deficient aged mice develop glucose intolerance and a reduced β -cell area (Jain et al., 2012). Therefore, DJ-1 is not only a recognized PD-associated protein, but it also might participate to glucose homeostasis and diabetes onset, and the recent discovery of DJ-1 as a novel deglycase could help to understand its involvement in diabetes and post-diabetic diseases. As a matter of fact, glycation has been reported to favor diabetes complications, including atherosclerosis, hypertension, nephropathy, cataracts, retinopathy, and cardiomyopathy. Therefore, the deglycating function of DJ-1 might represent a protective mechanism to limit glycation side effects and the development of diabetic complications.

The results concerning the deglycase activity of DJ-1 appear compelling even though further experiments are required to confirm this novel role associated with the protein. Specifically, *in vivo* data are highly awaited to assess whether the deglycase activity occurs under physiological conditions. Actually, besides biochemical assays, the activity has been demonstrated only in bacteria and human-derived cell cultures (Abdallah et al., 2016; Advvedissian et al., 2016). Indeed, authors utilized *Escherichia coli* mutants for DJ-1 homologues, named hchA, yhbO, and yajL, showing that they have higher glycation content at DNA and RNA levels compared to wild type strains. Furthermore, triple mutants for DJ-1 homologues have 2.5 times more glycation level than mutants for proteins belonging to the system of glycated DNA repair, suggesting that the bacterial DJ-1 homologues play an important role in glycated DNA repair

(Richarme et al., 2017). Consistent with these results, Advedissian and colleagues have showed that cultured human keratinocytes, in which DJ-1 has been silenced by siRNA, are characterized by increased glycation, while the overexpression of DJ-1 promotes a reduction of AGEs level (Advedissian et al., 2016). It is worth mentioning that some contrasting findings have been also reported. Indeed, Pfaff and co-workers were not able to observe any deglycating activity, *in vitro*, using both human DJ-1 and *D. melanogaster* homologue DJ-1 β . Moreover, they did not reveal accumulation of glycated proteins in their DJ-1 β null fly model compared to wild-type flies, suggesting that DJ-1 β might not participate in protein deglycation (Pfaff et al., 2017). In the light of these findings, to better characterize this function *in vivo*, future experiments should be performed using mammalian model organisms, in which there is only one single DJ-1 homologue, differently from bacteria and flies. For example, under DJ-1 depletion, it would be expected that mammals present a higher accumulation of glycated biomolecules, while, on the other hand, its overexpression should reduce carbonyl damages. To address this point, the discovery that some small molecules are able to increase the levels of DJ-1 can be very useful. For instance, Zhou et al. (2011) have reported that phenylbutyrate, a histone deacetylase inhibitor, is able to enhance DJ-1 expression, *in vivo*, promoting protection to dopaminergic neurons against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) toxin. In contrast, in DJ-1 knockout mice, the same compound did not more explicate any protective function, indicating that its action is dependent on the presence of DJ-1. Therefore, phenylbutyrate might represent a suitable molecule to up-regulate the DJ-1 expression *in vivo*, allowing the investigation of its deglycase activity. Another compound, which has been described to enhance the expression of DJ-1, is the isothiocyanate sulforaphane, extracted from cruciferous vegetables (Advedissian et al., 2016). Specifically, this molecule has been demonstrated to stimulate the expression of protective enzymes, among which DJ-1, and to decreased protein glycation in HaCaT keratinocytes (Advedissian et al., 2016). Conjointly to experiments in animal models, it would be interesting to evaluate whether PD patients with DJ-1 mutations present higher glycation level and are more prone to develop diabetes.

To summarize, as represented in **Figure 1**, the proposed deglycase activity of DJ-1 could explain several features that have been attributed to the protein so far. Moreover, a great novelty of these findings is that DJ-1 may represent the first identified enzyme able to restore both proteins and nucleic acids after glycation damages, since no other protein has been yet identified with this ability. Although this activity requires further confirmations, especially *in vivo*, the recent discoveries discussed here might shed light on a novel aspect of the physiological function of DJ-1, attempting to clarify the multifaceted nature of this protein.

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Accepted: 2017-11-04

doi: 10.4103/1673-5374.219035.

How to cite this article: De Lazzari F, Bisaglia M (2017) DJ-1 as a deglycating enzyme: a unique function to explain a multifaceted protein? *Neural Regen Res* 12(11):1797-1798.

Plagiarism check: Checked twice by iThenticate.

Peer review: Externally peer reviewed.

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Open peer review report:

Reviewer: Abhisek Mukherjee, University of Texas Health Science Center at Houston, USA.

Comments to authors: Assuming that this paper is a commentary on recent work published by Richarme et al. (2017), I think the author concisely describes

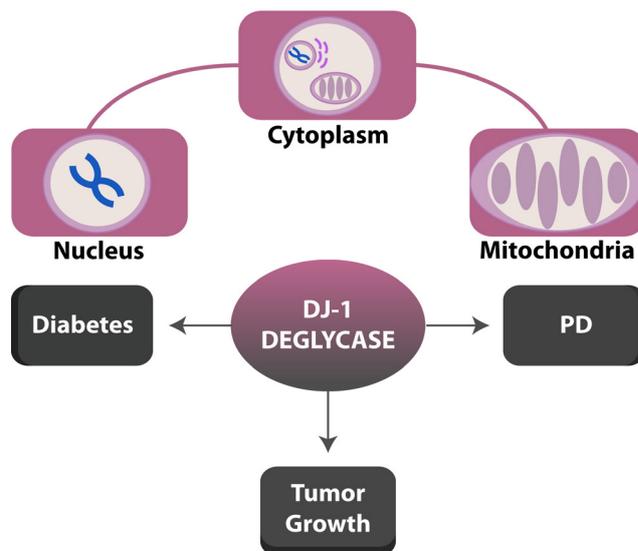


Figure 1 The recently reported deglycating activity of DJ-1 reconciles several features previously described for the protein.

The deglycating activity reported for DJ-1 may explain its different subcellular localizations, indeed the protein has been found in the cytoplasm, nucleus, and mitochondria. Moreover, this proposed activity could help to understand the involvement of the protein in Parkinson's disease (PD), tumor growth and diabetes.

the importance of the findings and precisely describes the limitations.

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