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EDITORIAL HIGHLIGHT

Peroxiredoxin 5 links mitochondrial redox signalling with calcium dynamics: impact on Parkinson's disease

Gavin P. Davey* and Juan P. Bolaños†

*School of Biochemistry and Immunology, Trinity Biomedical Sciences Institute, Trinity College Dublin, Dublin, Ireland

†Institute of Functional Biology and Genomics (IBFG), Department of Biochemistry and Molecular Biology, University of Salamanca-CSIC, IBSAL, Salamanca, Spain

Read the full article '*Mitochondrial peroxiredoxin-5 as potential modulator of mitochondria-ER crosstalk in MPP$^+$-induced cell death*' on page 473.

Preventing and reversing mitochondrial dysfunction in the neuron is a widely pursued objective in neurodegeneration research. Neurons rely on mitochondria to synthesize ATP, and a large body of evidence suggests that mitochondrial regulation of oxidative stress and Ca^{2+} homeostasis is essential for controlling the neurodegenerative process. The molecular mechanisms that give rise to defective activities of the mitochondrial electron transport chain (ETC) complexes present in brain disorders such as Parkinson's disease and Alzheimer's disease remain unknown. However, aberrant aggregation of proteins, such as α-synuclein and ß-amyloid, are known to interact with ETC complexes and reduce their activities. Neurotoxins, such as the Parkinsonian-inducing compound, 1-methyl-4-phenylpyridinium (MPP^+), have been invaluable agents in exploring the relationship between oxidative phosphorylation, Ca^{2+} homeostasis and reactive oxygen species (ROS) in the dopaminergic neuron.

Amongst the important regulators of mitochondrial ROS are superoxide dismutase and glutathione peroxidase, as they control superoxide and peroxide levels respectively. Recently, the peroxiredoxin antioxidant enzyme family was found to scavenge peroxide and, hence, to control oxidative stress in neurons through the use of redox active cysteine(s) within their active site, that becomes oxidized to sulphenic acid. The oxidized peroxiredoxin in turn may be recycled to a reduced state by interacting with thioredoxins.

One of the peroxiredoxins that localizes both in mitochondria and cytoplasm, peroxiredoxin 5 (PRDX5), reacts more efficiently with peroxynitrite and organic peroxides than other peroxiredoxins. Peroxynitrite ($ONOO^-$) plays a critical role in mitochondrial ETC damage and regulation of this highly reactive nitrogen species may be neuroprotective. (Bolaños and Heales 2010). In a previous study, it was found that PRDX5-deficient SH-SY5Y neuroblastoma cells are more vulnerable to the Parkinsonian-inducing toxin MPP^+ (De Simoni *et al.* 2008); however, the precise molecular mechanism whereby PRDX5 could exert neuroprotection remained elusive. In the article by De Simoni, 2013 in the *Journal of Neurochemistry* (DOI: 10.1111/jnc.12117), the authors followed up these observations using the inverse strategy of stably expressing the human mitochondrial form of PRDX5 in SH-SY5Y cells. In a comprehensive series of experiments, the involvement of PRDX5 in linking mitochondrial redox signalling with endoplasmic reticulum (ER)-mitochondrial Ca^{2+} dynamics was monitored in response to the Parkinsonian-inducing toxin, MPP^+. They found that PRDX5 reduced MPP^+-induced cytotoxicity, as assayed by LDH release, ATP, ROS and 3-nitrotyrosine production (as an index of reactive nitrogen species), suggesting a role for this isoform in controlling the rate of apoptosis in these cells. This antiapoptotic effect was confirmed by experiments showing the reversal of MPP^+-induced changes in mitochondrial DNA (mtDNA) damage, caspases-3 and -9 activation and apoptotic nuclei. Further experiments revealed the ability of PRDX5 to abolish the increase in intracellular Ca^{2+}, prevent calpain activation and markedly reduce the production of pro-apoptotic tBax in MPP^+-treated cells. Next, the authors explored the MPP^+-induced effects on Ca^{2+} dynamics by using nimodipine to inhibit L-type voltage–dependent calcium channels in the plasma membrane,

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Address correspondence and reprint requests to Juan P. Bolaños, Institute of Functional Biology and Genomics (IBFG), Department of Biochemistry and Molecular Biology, University of Salamanca-CSIC, Salamanca, Spain. E-mail: jbolanos@usal.es

Abbreviations used: ER, endoplasmic reticulum; ETC, electron transport chain; MPP^+, 1-methyl-4-phenylpyridinium; ROS, reactive oxygen species.

dantrolene to inhibit ryanodine receptors (RyRs) in the ER and 2-aminoethoxy diphenyl borate to inhibit inositol-1,4,5-trisphosphate receptors (IP_3Rs) in the ER. The results showed that 2-aminoethoxy diphenyl borate significantly counteracted loss of cell viability in response to MPP^+ as well as nearly totally preventing the increase in cytosolic Ca^{2+}, similar to over-expression of mitochondrial PRDX5. Thus, mitochondrial PRDX5 is revealed as a viable target for neuroprotection through its ability to control ROS/reactive nitrogen species generation as well as Ca^{2+} dysregulation (Fig. 1).

The results of De Simoni and colleagues (De Simoni *et al.* 2013) fit within the interesting growing field of peroxiredoxins being regulators of dopaminergic degeneration in Parkinson's disease (PD). Thus, a role for peroxiredoxin in this disorder has been suggested to involve phosphorylation of the PRDX2 isoform in nigral neurons in *post-mortem* tissue from PD patients (Qu *et al.* 2007). PRDX1 over-expression protects against 6-hydroxydopamine (6-OHDA)-induced Parkinsonism in cell culture models (Lee *et al.* 2006). Interestingly, the relatively low levels of PRDX5 in dopaminergic neurons may be an important reason why these neurons are less resistant to toxic stress than other neurons in the brain. Likewise, these findings raise a number of interesting possibilities. For example, follow-up experiments should now focus on the ability of PRDX5 to prevent neurotoxicity in both primary neurons and in PD-patient-specific iPS-derived dopaminergic neurons. Overall, the fact that PRDX5 clearly affects Ca^{2+} dynamics is also important in the light of the new anti-Parkinsonian therapeutics that regulate Ca^{2+} transport. The further involvement of PRDX5 in regulating Ca^{2+} dynamics in dopaminergic neurons remains to be seen.

A number of tantalizing implications come to mind in light of recent research on mitochondrial transport and Ca^{2+} dynamics in the neuron. The recent focus on mitochondrial fusion and fission events, and interactions with the ER has opened up an exciting area of neuronal biology. The fact that PRDX5 controls redox signalling in the mitochondrion and Ca^{2+} dynamics suggests it may have a role in post-translation modification of key mitochondrial fusion/fission and transport proteins. The effect of mitochondrial PRDX5 on complex I activity must be clarified as this defect of the ETC is an important observation in idiopathic PD (Schapira *et al.* 1989); the possibility that PRDX5-related redox signalling may control individual complex I subunit activity might be relevant to the disease pathology. Finally, mitochondrial heterogeneity within neurons and other cell types in the brain may relate to PRDX5 subcellular distribution. Mitochondria that reside in the nerve terminal region in the pre-synaptic neuron are known to have lower complex I energy thresholds than mitochondria from other origin (Telford *et al.* 2009), and seem to be more susceptible to neurotoxin-induced damage. Therefore, it would be interesting to analyse such mitochondria for the abundance of PRDX5 and other peroxiredoxins.

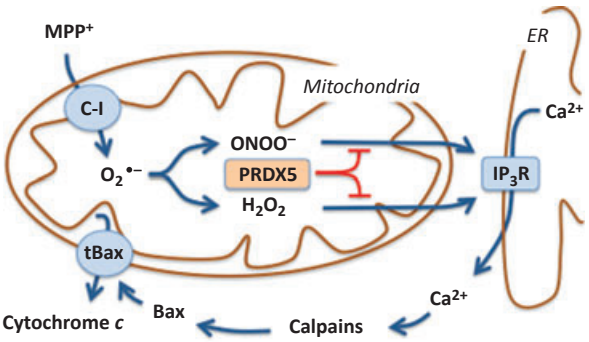

Fig. 1 Modulatory role of PRDX5 in mitochondrial-ER Ca^{2+} dynamics. Following mitochondrial complex I inhibition, such as that induced by 1-methyl-4-phenylpyridinium in SH-SY5Y cells, superoxide-mediated reactive oxygen species/reactive nitrogen species activate IP_3R to stimulate Ca^{2+} release from the ER. ER-released Ca^{2+}, through a calpain-Bax-tBax signalling pathway, promotes cytochrome *c* release from mitochondria. This pathway is down-modulated by PRDX5, hence linking PRDX5 to Ca^{2+} dynamics and, possibly, Parkinson's disease.

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