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Comment on "S-Nitrosylation of Parkin Regulates Ubiquitination and Compromises Parkin's Protective Function"

A very important aim for research into neurodegenerative diseases typified by misfolded proteins, such as Parkinson's disease (PD) and Alzheimer's disease, is to explain how environmental stress can produce the common "sporadic" forms of these disorders, thereby mimicking rare genetic mutations that cause the same phenotype. Recently, an elegant report by Chung *et al.* (1) shed some light on this enigma for PD, showing that nitric oxide (NO), a free-radical gas that can injure neurons, chemically combines through a reaction known as S-nitrosylation with the protein parkin, a ubiquitin E3 ligase that is known to cause some forms of PD when mutated. These authors also found that overexpression of parkin rescued neuronal cell lines under tissue-culture conditions subjected to proteasome inhibition and that this protective effect was abrogated by S-nitrosylation of parkin, thus supporting the pathophysiological relevance of this chemical reaction. Additionally, a hallmark of sporadic PD is the formation of ubiquitinated inclusions of misfolded proteins known as Lewy bodies. However, Chung *et al.* found that S-nitrosylation of parkin decreased its E3 ligase activity, thereby inhibiting ubiquitination and Lewy-body formation. Hence, these findings do not fully account for the signs encountered in sporadic PD.

Concomitantly, our laboratory reported similar findings with regard to S-nitrosylation of parkin, including the fact that S-nitrosylated parkin (dubbed SNO-PARK) is present at detectable levels in human brains of patients with PD (2). However, we found that S-nitrosylation increased, rather than decreased, the ubiquitin E3 ligase activity of parkin. Several technical differences may explain the apparent discrepancy between our results and those of Chung *et al.* We found that the effect of nitrosylation was time dependent. Within the first few hours of S-nitrosylation of parkin, we observed increased ubiquitin E3 ligase activity for both parkin itself (representing autoubiquitination) and other substrates such as synphilin-1, which can be a component of Lewy bodies. This increased E3 ligase activity was followed by a gradual decrease in activity. Therefore, we feel that our observation of an initial increase in parkin E3 ligase activity can be explained by our looking at earlier time points after S-nitrosylation than did Chung *et al.* Other methodological differences in the E3 ligase assays may also account for the difference, such as our inclusion of a proteasome inhibitor in the E3 ligase assay to prevent catabolism of ubiquitinated substrates (such as parkin) during the assay and to allow for their detection.

Our observation of an early increase in the ubiquitin E3 ligase activity of parkin after S-nitrosylation reinforces the potential importance to sporadic PD of this chemical modification; it helps account not only for the adverse effect of S-nitrosylation of parkin on the survival of neurons (1) but also for the appearance of Lewy bodies in the disease process (2). Nonetheless, a note of caution is in order in interpreting these findings, as much of the data from both our study and that of the Dawson laboratory are based on tissue culture and animal models of PD. Although both groups detected SNO-PARK in human brains of sporadic PD patients, the quantitative level of nitrosylated protein remains unknown, and its exact contribution to the disease process in humans awaits further study. However, the contribution of S-nitrosylated proteins to physiological and pathophysiological processes, including sporadic PD, remains a very hot topic in research into neurodegenerative disorders.

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References and Notes

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2. D. Yao *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **101**, 10810 (2004).
3. We thank the Dawson laboratory for sharing details of their methods with us in order to discern the difference between our two studies.

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