A balancing act in Parkinson's disease: Phosphorylation of alpha-synuclein

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Both genetic and pathologic data indicate a role for the neuronal protein alpha-synuclein in Parkinson disease. Previous studies have indicated that phosphorylation of alpha-synuclein at amino acid 129 (Ser129) is a key event in alpha-synuclein-mediated nerve cell toxicity. However, Mel Feany and colleagues, at Brigham and Women's Hospital, Boston, have now identified a counterbalancing role in nerve cell protection for phosphorylation of alpha-synuclein amino acid 125 (Tyr125).

In the study, phosphorylation of human alpha-synuclein Tyr125 was detected in Drosophila transgenic for human alpha-synuclein and shown to protect from alpha-synuclein-mediated nerve cell toxicity in a Drosophila model of Parkinson disease. That the two phosphorylated amino acids have opposing roles was indicated by the observation that Tyr125 phosphorylation decreased levels of toxic soluble alpha-synuclein oligomers in the Drosophila brain, whereas Ser129 phosphorylation increased them.

More importantly, Tyr125 phosphorylation was found to decrease as both humans and Drosophila aged and was reduced in cortical tissue from patients with synucleinopathy dementia with Lewy bodies, a disease related to Parkinson disease. The authors therefore suggest that changes in the balance between Ser129 and Tyr125 phosphorylation — which promote nerve cell toxicity and protection, respectively — might cause alpha-synuclein-mediated nerve cell toxicity in Parkinson disease and related disorders.