OPEN PEER REVIEW REPORT 1

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Title: Soluble Alpha-synuclein Post-translational Modifications: Unexpected Regulators of Alpha-synuclein Amplification
Reviewer's Name: Francisco Cayabyab
Reviewer's country: Canada

COMMENTS TO AUTHORS

The Perspective article summarized their recent report (Zhang et al., Nature Neurosci, 2023) that soluble α-syn undergoes post-translational modifications (PTMs) that can affect the seeding property and amplification of pathological α-syn in different synucleinopathies. Whereas previous studies concentrated on the PTMs of pathological α-syn (i.e., the seed), this group has identified for the first time the numerous PTMs of soluble α-syn from control brains and different synucleinopathy brains (e.g., MSA, LBD, and LBD with dementia). In particular, these investigators have identified 51 PTM sites, with 34 of these occurring in the N-terminal region of soluble α-syn. They have analyzed 11 of these PTMs (as summarized in Table 1), with phosphorylation and acetylation having distinct effects on amplification and seeding of pathological α-syn. Overall, the authors conclude that these novel PTMs of soluble α-syn could be harnessed as neuroprotective targets for diverse synucleinopathies, and these PTMs could also have further implications and applications for other neurodegenerative diseases such as tauopathies. The authors also discussed other types of PTMs (e.g., arginylation, glycation, methylation, dimethylation). As a minor comment, it would be informative to name the specific sites of these yet uncharacterized PTMs (either add to the Table 1 or mention in text, for example, as already mentioned by the authors for the two O-GlcNAc sites: T54 and T75; arginylation: E57; methylation/dimethylation: K12, K21, K58, K60, and K96). Also, in addition to the effects on amplification and seeding property, the authors should briefly discuss possible implications of these novel PTMs on α-syn localization, function and signaling pathways (altered protein-protein interactions) for future studies.