The baker, sugar, and the molecular basis of Parkinson's disease
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Aggregation of alpha-synuclein (ASYN) in Lewy bodies and Lewy neurites is the typical pathological hallmark of Parkinson's disease (PD) and other synucleinopathies. Furthermore, mutations in the gene encoding for ASYN are associated with familial and sporadic forms of PD, suggesting this protein plays a central role in the disease. However, the precise contribution of ASYN to neuronal dysfunction and death is unclear. There is intense debate on the nature of the toxic species of ASYN, and little is still known about the molecular determinants of oligomerization and aggregation of ASYN in the cell. Harnessing the power of various model organisms, we are making progress towards the understanding of the basic molecular mechanisms underlying PD and other synucleinopathies. In order to clarify the effects of different posttranslational modifications on the toxicity and aggregation of ASYN, we employ a variety of model systems. Phosphorylation and glycation are emerging as important modifications affecting ASYN aggregation. Altogether, our data shed light into the molecular underpinnings of PD, and open novel perspectives for therapeutic intervention in synucleinopathies.