Posttranslational modifications: modulators of alpha-synuclein biology and pathobiology

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Résumé

The aggregation of alpha-synuclein (ASYN) in Lewy bodies and Lewy neurites is the typical pathological hallmark of Parkinson's disease (PD) and other neurodegenerative disorders commonly known as synucleinopathies. Furthermore, mutations in the gene *SNCA*, encoding for ASYN, are associated with both familial and sporadic forms of PD, further supporting the hypothesis that this protein plays a central role in the disease. However, the precise contribution of ASYN to neuronal dysfunction and death is still 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 context of a living cell. This is extremely important as it may help explain the formation of different types of ASYN aggregates, which may be characteristic of different synucleinopathies.
Posttranslational modifications (PTMs) are chemical alterations that proteins undergo during their lifetime. They are tools evolved by biological systems in order to increase the complexity of proteomes, and they modulate protein folding, localization, and function. They are particularly relevant in the context of intrinsically disordered proteins (IDPs), such as ASYN, as they may modulate the folding of specific domains or of the whole protein.

By taking advantage of studies in various model organisms, we are investigating the effect of various PTMs on the toxicity and aggregation of ASYN. We found that glycation and acetylation are emerging as important PTMs that affect the aggregation of ASYN.

Acetylation is a reversible PTM that may regulate protein function and subcellular localization. While ASYN is known to be N-terminally acetylated, it was not known to undergo acetylation in other residues. Using mass spectrometry, we found that ASYN can be acetylated on lysine (K) 6 and K10, in rat and mouse brain tissue. Strikingly, we discovered that ASYN interacts with and is a substrate of SIRT2, a class III NAD-dependent deacetylase. Using acetylation-mimetic (KQ) and acetylation-dead (KR) mutants, we found that acetylation reduces ASYN aggregation both in vitro, using recombinant protein, and in cell models. Interestingly, we found that overexpression of acetylation-dead (KR) mutants, using adeno-associated viral vectors stereotactically injected into the substantia nigra in the rat brain,

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increased the loss of dopaminergic (TH)-positive neurons, suggesting blocking acetylation exacerbates ASYN toxicity in vivo.

Another PTM we hypothesized to be relevant in the context of PD is glycation, a chemical reaction of sugars with proteins or nucleic acids. Glycation is typically an irreversible, age-associated PTM, that damages proteins. We detected the presence of glycated ASYN in post-mortem human brain tissue from PD patients. Next, we found that glycation promotes the oligomerization of ASYN in vitro, but not its fibrilization. In various cellular models expressing human ASYN, ranging from yeast to patient-derived induced-pluripotent stem cells (iPSCs), we found that glycating conditions exacerbated the toxicity of ASYN. In ASYN transgenic mice, we also confirmed that methylglyoxal (MGO), a strong glycating agent, induced dopaminergic cell loss in the substantia nigra.

Using cell models for mechanistic studies, we found that glycation blocks lysine resides that are normally used to target the protein for degradation by the proteasome, leading to an increase in its half-life and, therefore, to its accumulation. Importantly, we found that MGO-scavengers reduce ASYN toxicity in cell models and in ASYN-transgenic flies, suggesting blocking glycation might constitute a possible therapeutic strategy.

In total, our data shed new light into the molecular underpinnings of synucleinopathies, opening novel perspectives for future therapeutic interventions.

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Mots-Clés: posttranslational modifications, alpha, synuclein, Parkinson