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The role of phosphorylation in alpha-synucleinothies

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Multiple lines of evidence indicate that post-translational modifications (PTMs) of α-synuclein (α-Syn) play an important role in modulating pathology in Parkinson's disease (PD) and α-synucleinothies[1]. Disease-associated α-Syn amyloid fibril are often phosphorylated and accumulate in Lewy bodies[2,3]. However, it is unclear how phosphorylation relates to α-Syn pathology.

Here, by combining protein expression and chemical synthesis, we obtained homogeneous α-Syn with phosphorylation at specific sites (such as Tyr39, Ser129), which were found to be phosphorylated in the body and are highly correlated with the pathological changes. The results showed that phosphorylation at Tyr39 (pY39 α-Syn) and Ser129 (pS129 α-Syn) induces α-Syn to form a distinct fibril with different structures and higher cytotoxicity compared with the wild-type α-Syn[4,5]. In addition, the phosphorylation of Ser129 modulate the propagation properties of α-Syn and induce pS129 α-Syn to form different stain[5]. The polymorphism of α-Syn stains may provide an explanation for high diversity of pathogenetic process. On the other hand, through cryo-electron microscopy (cryo-EM), we found that the entire N-terminus of pY39 α-Syn is involved into the fibril core, which may lead to the inability of molecular chaperones to mediate its clearance or protect α-Syn from protease digestion[4]. These works illuminate the importance of PTMs in structure of amyloid aggregation and provide insight into the pathology of phosphorylated α-Syn in the progression of PD and α-synucleinothies.

References

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