Phosphorylation Induces α-synuclein to Form Different Strains

Yan-Mei Li, *[a]

[a] *Department of Chemistry, Tsinghua University, Beijing, China.*
E-mail: liym@mail.tsinghua.edu.cn

α-synuclein (α-syn) is a pathologically related protein, which exists in multiple neurodegenerative diseases. Phosphorylation, as a post-translational modification, has been proposed to regulate the process of synucleinopathies. However, it remains unclear that how phosphorylation at specific sites regulates the structure and properties of α-synuclein and how it further affects the process of disease. In this series of work, we synthesized homogeneous α-synuclein with phosphorylation at a single site (pS129, pY39) using two-fragment and three-fragment method of expression protein ligation strategy, respectively. For serine 129, phosphorylation changes strains of α-syn fibrils, leading to different fibril characteristics, higher cellular toxicity[1] and significantly enhances the binding affinity of α-syn preformed fibrils (PFF) with receptors on cell surface, which affects the cell-to-cell transmission of α-synuclein.[2] For tyrosine 39, cryo-EM structure determination revealed that phosphorylation results in a rearrangement of amyloid fibril structure. The structure presents a distinct fibril core with a hydrophilic channel in the core center, suggesting the unique role of pY39 in synucleinopathies.[3] This series of work illuminates the role of phosphorylation at specific site in the regulation of α-syn fibril structure and pathological properties, and highlights the importance of posttranslational modifications in the progression of degenerative diseases.

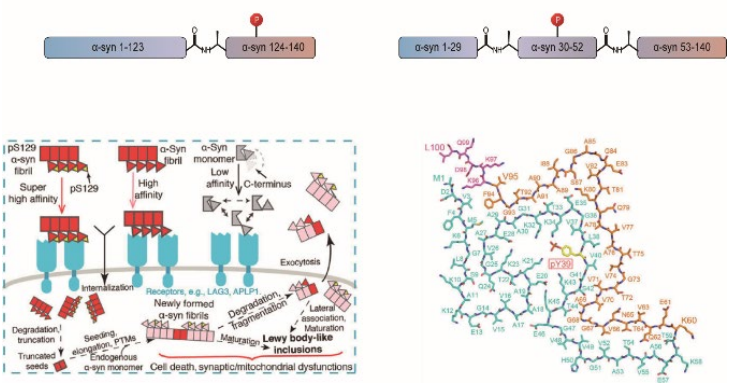

Figure 1. Phosphorylation at specific sites influences α-syn fibril structure and properties.Left: pS129 enhances α-syn pathological transmission.[2] Right: pY39 rearranges α-syn fibril structure.[3]

References

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