Interdisciplinary insights into the influence of lipids on the formation of α-synuclein fibrils in Parkinson's disease

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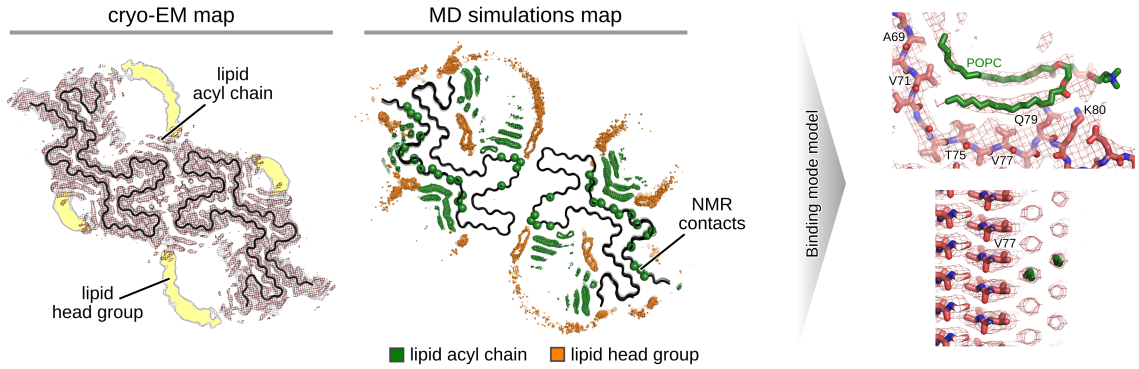

Parkinson's disease is the second most common neurodegenerative disease globally, and recent estimates suggest that more than ten million people worldwide suffer from it [1]. In this disease, α-synuclein proteins form thread-like structures called fibrils. When these fibrils clump together into Lewy bodies, the characteristic pathological hallmark of Parkinson's, they probably damage nerve cells [2]. Studies on the composition of Lewy bodies extracted postmortem from brain tissue of Parkinson's patients revealed that lipids and membranous organelles are also significant components [3]. However, although interactions between α-synuclein fibrils and lipids have been identified as relevant for Parkinson's pathogenesis, any molecular insights into their interactions have remained elusive.

Using cryo-electron microscopy, we visualized how lipid molecules bind to the fibril surface for the first time, thereby connecting the individual subunits [4]. Complemented by molecular dynamics simulations combined with solid-state nuclear magnetic resonance spectroscopy, we show how the lipid and protein elements interact within fibrils [4]. Together with our previous studies [5], these insights also indicate a mechanism for fibril-induced lipid extraction, which is likely to be involved in the development of Parkinson's. Specifically, one potential mechanism for cellular toxicity is the disruption of intracellular vesicles mediated by α-synuclein fibrils and oligomers, and therefore the modulation of these interactions may provide a promising strategy for future therapeutic interventions [6].

[1] Parkinson's foundation (https://www.parkinson.org/understanding-parkinsons/statistics)
[2] W. Poewe, *et al.*, *Nat. Rev. Dis. Primers*, **2017**, 3, e17013.
[3] S.H. Shahmoradian, *et al*, *Nat. Neurosci.*, **2019**, 22, 1099-1209.
[4] B. Frieg, *et al.*, *Nat. Commun.*, **2022**, 13, e6810.
[5] L. Antonschmidt, *et al.*, *Sci. Adv.*, **2021**, 7, e2174.
[6] L. Antonschmidt, *et al.*, *Nat. Commun.*, **2022**, 13, e5385.