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COMPetitive PAiring StatisticS (COMPASS) for Protein Structural Analysis: Insights Into α-Synuclein Conformational Changes Upon Liquid-Liquid Phase Separation

C. Iacobucci[1,2,3], Daniele Ubbiali[2,3], and Andrea Sinz[2,3]

1) Department of Physical and Chemical Sciences, University of L'Aquila, Via Vetoio, Coppito, 67100 L'Aquila (Italy)
2) Department of Pharmaceutical Chemistry and Bioanalytics, Institute of Pharmacy, Martin Luther University Halle-Wittenberg Kurt-Mothes-Str. 3, 06120 Halle/Saale (Germany)
3) Center for Structural Mass Spectrometry, Martin Luther University Halle-Wittenberg, Kurt-Mothes-Str. 3, 06120 Halle/Saale (Germany)

α-Synuclein (α-syn) is an intrinsically disordered protein (IDP) that undergoes liquid-liquid phase separation (LLPS), fibrillation, and forms insoluble intracellular Lewy bodies in neurons, which are the hallmark of Parkinson's Disease (PD). Neurotoxicity precedes the formation of aggregates and might be related to α-syn LLPS. The molecular mechanisms underlying the early stages of LLPS are still elusive.

To obtain structural insights into α-syn upon LLPS, we take advantage of cross-linking/mass spectrometry (XL–MS) and introduce an innovative approach, termed COMPASS (COMPetitive PAiring StatisticS). In this presentation, COMPASS method will be introduced and its application on α-syn described. In fact, COMPASS revealed that the conformational ensemble of α-syn shifts from a "hairpin-like" structure towards more "elongated" conformational states upon LLPS.[1]

We obtain insights into the critical initial stages of LLPS and establish a novel mass spectrometry-based approach that will aid to solve open questions in LLPS structural biology.

References

1. D. Ubbiali, M. Fratini, L. Piersimoni, C. H. Ihling, M. Kipping, I. Heilmann, C. Iacobucci, A. Sinz; Angew. Chem. Int. Ed., **134**, e202205726 (2022).