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Beyond SAXS, how do we predict misfolding hotspots in alpha-synuclein?

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The 140 residue intrinsically disordered protein -synuclein (-syn) misfolds to form fibrils that are the major constituent of the Lewy body intracellular protein inclusions and neurotoxic oligomers occurring in a number of neurodegenerative diseases, including Parkinson's disease (PD) and dementia with Lewy bodies. Using SAXS data analysed by ensemble optimised modelling (EOM) we have been able to show that the wild-type (WT) -syn gives a bimodal distribution of Rg and Dmax whose relative proportions are varied in the three pathological single point mutations. Residual dipolar couplings (RDCs) determined by 14N1H-HSQC NMR for the WT have been useful in explaining the role of long range interactions in folding, but have not been applied to understanding the behaviour of the familial mutants. To study the familial mutants and those yet to be discovered, amino acid replacement scanning of the whole -syn sequence to determine possible misfolding "hot spots" and perform SAXS-EOM and 14N1H-HSQC NMR would be a huge task. However, it has been shown that it is possible to simulate RDCs from the sequence of intrinsically disordered proteins using the Flexible Meccano and Pales software. In this presentation, we shall show how simulated RDCs, validated by our historic SAXS data can suggest regions where changes in long and short range interactions can lead to misfolding. Thus forearmed, we can tackle the challenges of experimental validation.

Keywords or phrases (comma separated)

SAXS, EOM, Parkinsons Disease, residual dipolar couplings

Summary

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