Contribution ID: **513** Type: **Poster**

Structure and Dynamics of Huntingtin. A Segmental Labelling Approach

Monday 20 March 2023 16:00 (2 hours)

Huntington's Disease (HD) is a genetically inheritable neurodegenerative disorder caused by a mutation in the gene encoding the protein Huntingtin (Htt). The mutation causes an increase in CAG trinucleotides in the first exon, which increases the number of glutamines in the poly-glutamine (Poly-Q) tract of the intrinsically disordered N-terminal region of the protein. HD symptoms only manifest in individuals with a poly-Q tract of more than 35 consecutive glutamines. The length of the Poly-Q tract beyond the threshold is correlated with the age of onset and the severity of the pathology. The exon-1 of Htt is a low complexity region that contains the N-terminal 17 residues, the poly-Q tract and a proline rich region. My project aims at elucidating the structural differences between non-pathogenic and pathogenic Htt exon-1 constructs using Small-Angle Neutron Scattering (SANS) measurements in amino-acid specific deuterated samples. Profiting of the distinct scattering properties of deuterium and hydrogen, we aim at extracting valuable structural information of the Poly-Q region. Constructs with specific deuteration patterns (Gln/Pro) are produced using the Cell-Free protein expression system. Cell-Free expression is used to control the animo acid composition and avoid secondary effects of the expression such as scrambling, in order to avoid isotopologues of partly deuterated protein samples.
SANS data, collected at the D22 Beamline at ILL, and Small-Angle X-ray Scattering (SAXS) data measured at Soleil and ESRF Synchrotrons are combined with atomistic models to derive unique structural information of different Htt constructs. Synergistic analyses of the data are performed using the ensemble optimization method (EOM). Currently, eleven SANS samples have been measured for pathogenic (HttQ36) and non-pathogenic (HttQ16) constructs of the protein and ensemble analyses are in progress.

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Session Classification: Poster Session MONDAY

Track Classification: Micro-Symposium DEUNET