

ORAL PRESENTATION O1

Multi-domain protein aggregation : a novel mechanism by which polyglutamine repeat proteins aggregate

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Protein aggregation plays a major role in many neurodegenerative diseases including Alzheimer's and Huntington's disease. Ataxin-3 is an intracellular protein with a C terminal polyglutamine repeat tract. Expansion of the polyglutamine tract to over 45 consecutive glutamines causes the disease spinocerebellar ataxia type-3. The expanded polyglutamine protein forms aggregates within the nucleus, a process intrinsically linked to disease pathogenesis. Our aim is to use a range of protein engineering, spectroscopic and biochemical methods to determine the kinetic and structural basis for ataxin-3 aggregation. Our data shows that the structure and stability of ataxin-3 does not change with polyglutamine tract length. Strikingly we demonstrate that ataxin-3 aggregation involves not only the polyglutamine tract but other folded domains of the protein. Through H/D exchange and NMR experiments we have identified regions of the protein which are involved in the early stages of ataxin-3 aggregation. Furthermore, we show that some of the physiological binding partners of ataxin-3 play an important role in modulating the aggregation kinetics of ataxin-3. Our data enhances our general understanding of polyglutamine fibrillogenesis and highlights the role for nonpoly(Q) domains and binding partners in modulating the kinetics of misfolding and self-assembly in this family.