O-15.2 Invited speaker

Allosteric modulators of protein self-assembly: clues for therapeutic approaches in SCA3.

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Spinocerebellar ataxia type-3 (SCA3) is a rare inherited ataxia with no cure, caused by CAG repeat expansion in the ATXN3 gene, which leads to an expanded polyglutamine (PolyQ) tract in the ataxin-3 protein (Atx3). This expansion causes Atx3 to aggregate in degenerating brain regions through a complex self-assembly process initiated by an aggregation-prone region in its Josephin domain (JD). An interdisciplinary approach was used to study the effects of CLR01, a supramolecular binder of positively charged lysines and arginines, on Atx3 self-assembly. Our results indicate that CLR01 binds to JD in a region distant from the aggregation-prone region, reducing its flexibility and modulating Atx3 self-assembly pathways. Consistent with biophysical data, CLR01 decreases aggregation, reverses synaptic defects in neurons expressing polyQ-expanded Atx3, and improves motor function in SCA3 disease models. These findings highlight the potential for developing CLR01-derived allosteric modulators of pathogenic Atx3 aggregation, providing insights into new therapeutic approaches for SCA3 and other neurodegenerative diseases.