Mechanistic Elucidation of PolyQ Peptides Folding and Aggregation in Spinocerebellar Ataxias

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Abstract

A group of dominantly inherited ataxias with degenerative changes in the cerebellum are collectively referred to as spinocerebellar ataxia (SCA). Between the ages of 30 and 50, these conditions usually appear. The cerebellum is the part of the brain responsible for coordinating voluntary movements, whereas ataxia denotes a loss of balance and coordination. Although the indications and symptoms of SCAs might vary, they typically include dysarthria (speech difficulties), an irregular gait, and poor handwriting. Certain genetic mutations are associated with different subtypes of spinocerebellar ataxias.

We present our most recent results on the synthesis, purification, conformational analysis, folding, and aggregation of polyglutamine peptides from SCA2, SCA3, SCA6, and SCA7, with and without flanking sequences, based on a thorough biophysical investigation. We compared the average length of these SCAs with that of their extended equivalents. These polyglutamine peptides' aggregative nature makes it difficult to characterize them using NMR spectroscopy or single-crystal X-ray crystallography. Interestingly, vibrational spectroscopy (ATR-FTIR) offers the potential to examine these folding and aggregates under native in vitro conditions, even at very low concentrations. By analyzing the vibrational Amide I, II, III, and A bands, we can identify the conformations and aggregating behaviors under diverse molecular environments. IR spectroscopy enables the determination of the proportions of α-helical, β-sheet, and random coil secondary structures. Additionally, the Thioflavin T assay, dynamic light scattering (DLS), and filtration assays are used to investigate the aggregation of polyQ peptides and the size distribution of their aggregates. We have conducted thorough molecular dynamics (MD) simulations on both monomeric and aggregated versions of these polyQ peptides to gain

insight into their conformations and structural assemblies. Our findings demonstrate the critical relationship between aggregation, conformation, and sequence as well as the possible biological function of neurodegenerative polyQ peptides.

Keywords

Spinocerebellar Ataxia, PolyQ peptides, Folding, Aggregation, Neurodegenerative, inhibitors