PolyQ Tracts as Efficient C-capping Elements for Coiled-coils

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Poly-glutamine (polyQ) tract expansions have been linked to a variety of neurodegenerative diseases. The conservation of such sequences points to a relevant role, which is suggested to involve their organization into secondary structure elements. For the particular case of the androgen receptor (AR) we recently reported that the Leu-rich segment N-terminal to the polyQ tract acts as a helical N-capping sequence that propagates helicity into the tract itself [1]. Based on that, we have acquired *in vitro* CD and NMR as well as *in silico* MD data on a battery of peptides showing that the helicity of the sequence positively correlates with the number of glutamines in the tract up to the values found in the average human population (16-25 residues, depending on ethnicity), and that helix stabilization depends on glutamine sidechain-mediated hydrogen bonds. This supports a C-capping role for the polyQ tract, as a minimum number of glutamine residues is required to stabilize the helicity while further growth of the tract is detrimental because of increased aggregation rates. Proteome analysis shows that regions predicted to fold into coiled-coils are highly enriched in adjacent sequences N-terminal to polyQ tracts, thus providing the grounds for a general role of such tracts as C-caps for these helical elements.

[1] Eftekharzadeh et al. *Sequence Context Influences the Structure and Aggregation Behavior of a PolyQ Tract.* Biophys J. 2016 Jun 7;110(11):2361-6.