Putative Role of Hypercooperative Hydrogen Bonds in Stabilizing an Amyloid-Like Pathological Conformation of TDP-43, a Protein Linked to Amyotrophic Lateral Sclerosis

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As the world's population ages, a large increase in dementia is predicted for future decades. TDP-43, an essential RNA-binding protein, forms aggregates in >95% of sporadic ALS cases and is also tied to Alzheimer's Disease. TDP-43 is composed of a folded N-terminal domain, two central RRM RNA-binding domains, and a disordered, 150-residue long C-terminal region. The latter is essential for forming functional assemblies that regulate RNA translation but is also key for pathological aggregation. Previous studies showed that TDP-43 aggregates resist harsh treatment and seed new aggregates which spread and "infect" new cells [1]. The Gln/Asn rich motif (residues 341-367) of the C-terminal region is necessary for efficient aggregation of TDP-43 [2]. The objective of our work is to determine the structure of this aggregate and the basis of its stability. Utilizing extensive spectroscopic characterization and computational experiments, we propose that this motif forms a beta hairpin that oligomerizes to adopt an amyloid-like conformer. We also show that Gln and Asn side chain hydrogen bonds in amyloids may possess an extraordinary hypercooperativity, which could decisively stabilize TDP-43 aggregates. A study of TDP-43 aggregates from ALS patient brains showed that the Gln/Asn-rich motif is protected in vivo from Gln/Asn deamidation, Ser phosphorylation and Met oxidation [3], which is in line with our conformational model. The high conformational stability afforded by Gln/Asn H-bond hypercooperativity could explain the stability of these TDP-43 aggregates, and perhaps also those of other pathological amyloids, like polyglutamine aggregates, as well as functional amyloids like Sup35 (GNNQQNY) and CPEB3 (QQQQRQQQQ) implicated in memory consolidation.

References:
[1] Nonaka, T. et al. (2013) Cell Reports 4: 124-134.
[2] Budini, M. et al. (2015) Hum. Mol. Gene 24: 9-20.
[3] Kametani, F. et al. (2016) Sci. Reports 6: 23281.