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ALS protein dynamics highlight delicate balance between self-association and aggregation

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The ALS-related protein TDP-43 takes the first steps toward pathologic aggregation as part of its normal function, according to a new study publishing in the Open Access journal *PLOS Biology* on Jan. 6, 2016. The study, by Liangzhong Lim, Jianxing Song, and colleagues at the National University of Singapore, supports the emerging idea that protein aggregation in neurologic disease may be an exaggeration of the normal functions of the aggregating proteins.

Cytoplasmic aggregates of normal TDP-43 are found in almost all forms of amyotrophic lateral sclerosis (ALS), a fatal neurodegenerative disease affecting motor neurons, as well as in many cases of frontotemporal dementia (FTD). TDP-43 aggregation has been observed in ~97% of ALS and ~45% of FTD patients. It has also been implicated in a range of other neurodegenerative disorders, including, recently, Alzheimer's disease.

Study of the protein's biophysical properties, including aggregation dynamics, has been hampered by its strong propensity to aggregate, a problem the authors recently overcame by reducing salt concentrations in vitro. Here, they used a variety of spectroscopic and microscopic techniques to characterize in detail the structure of the C-terminal prion-like domain of TDP-43, and how the protein forms dynamic oligomers through interactions of the domain on separate protein molecules or by interacting with nucleic acid. While mutations of TDP-43 are a rare

cause of ALS, this prion-like domain hosts most of TDP-43's ALS-causing mutations. The authors showed that these mutations increase assembly and decrease disassembly of oligomers, tilting the balance toward aggregation into amyloid fibrils. The authors also discovered that a region of the protein that has previously been found to be necessary for toxicity promotes its association with membranes, which may increase aggregation propensity.

These results further highlight the delicate balance between normal function and pathology for aggregation-prone proteins such as TDP-43, and may help explain how aggregates of the non-mutated protein form in ALS. The authors also suggest that decreasing TDP-43's membrane-association potential "may represent a promising therapeutic strategy to treat neurodegenerative diseases."

More information: Lim L, Wei Y, Lu Y, Song J (2016) ALS-Causing Mutations Significantly Perturb the Self-Assembly and Interaction with Nucleic Acid of the Intrinsically Disordered Prion-Like Domain of TDP-43.*PLoS Biol* 14(1): e1002338. DOI: 10.1371/journal.pbio.1002338