Pathogenic motor neuron disease-linked mutations distinctly alter TDP-43 nanoscale dynamics

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Abstract

The hallmark of motor neuron disease (MND) pathology is the abnormal accumulation of insoluble proteins that form inclusions in motor neurons within the spinal cord and primary motor cortex. How, why, and when these proteins begin to aggregate has not been fully elucidated. In up to 97% of all MND cases, TAR DNA-binding protein-43 (TDP-43) is a key protein that is mislocalised from its native nuclear presence into cytoplasmic inclusions. Furthermore, genetic mutations in TDP-43 are implicated in familial MND, further linking the function of this protein to this neurodegenerative disease. The precise mechanism that drives the aggregation of TDP-43 in MND is unknown, however identifying the changes in the dynamics of the protein within the nucleus could shed light on how the different mutations contribute to its altered function in MND. We applied nanoscale single-molecule imaging to identify the changes in the dynamics and localisation of TDP-43 caused by well characterised pathogenic-causing mutation. We observe that the different pathogenic mutations uniquely influence the mobility of TDP-43. Most of the MND-linked mutations inhibit the movement of TDP-43 similar to how oxidative stressors such as arsenite induce inclusions of TDP-43 thereby immobilising the molecules. Furthermore, our data indicates that post-translational modifications in TDP-43 such as acetylation similarly restricts its dynamics within the nucleus. Together, our data suggests that the confinement of mobility of TDP-43 is a key step in the formation of toxic aggregates in disease.