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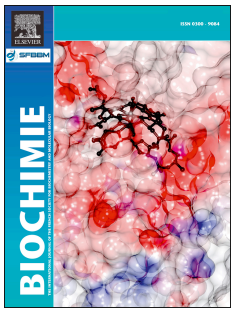

The amyloidogenicity of a C-terminal region of TDP-43 implicated in Amyotrophic Lateral Sclerosis can be affected by anions, acetylation and homodimerization

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Abstract

Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disease associated with accumulation of hyper-phosphorylated, and ubiquitinated TAR DNA-binding protein-43 (TDP-43) as inclusion deposits in neuronal cells. Recently, amyloid-like fibrillar aggregates of TDP-43 have been reported from several ALS patients. The C-terminal region of TDP-43 is central to TDP-43's pathological aggregation and most of the familial ALS mutations in the encoding *TARDBP* gene are located in this domain. Also, aberrant proteolytic cleavages of TDP-43 produce cytotoxic C-terminal fragments of ~ 15-35 kDa. The C-terminal end harbours a glycine-rich region and a Q/N rich prion-like aggregation-prone domain which has been shown to form amyloid-like fibrillar aggregates *in vitro*. Previously, TDP-43 protein has also been shown to undergo several other post-translational modifications such as acetylation and dimerization, however, their effects on TDP-43's amyloid-like *in vitro* aggregation have not been examined. Towards this, we have here examined effects of anions, acetylation and homodimerization on the *in vitro* aggregation of a C-terminal fragment (amino acid: 193-414) of TDP-43 termed TDP-43^{2C}. We find that kosmotropic anions greatly accelerate whereas chaotropic anions impede its aggregation. Also, we show that acetylations of certain lysines in C-terminal fragments significantly reduce the TDP-43^{2C}'s amyloid-like aggregation. Furthermore, we separated spontaneously formed cysteine-linked homodimers of the recombinantly purified TDP-43^{2C} using size-exclusion chromatography and found that these dimers retain amyloidogenicity. These findings would be of significance to the TDP-43 aggregation-induced pathology in ALS.