

Amyotrophic Lateral Sclerosis and the DNA Damage Response

<https://www.neurodegenerationresearch.eu/survey/amyotrophic-lateral-sclerosis-and-the-dna-damage-response/>

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United Kingdom

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Research Abstract

Amyotrophic Lateral Sclerosis (ALS) is caused by premature/accelerated degeneration of motor neurones. Whereas some cases of ALS are sporadic and of unknown molecular cause, others are due to hereditary dominant mutations in one of approximately eight genes. It has emerged recently that several of the proteins encoded by these genes are involved in regulating mRNA transcription, splicing, and stability, including Fused-in-Sarcoma/Translocated-in-Sarcoma (FUS/TLS) and TAR DNA-binding protein 43 (TDP-43). This raises the possibility that, in some cases of ALS, neuronal cell death may involve loss-of-function defects in RNA processing. However, how and why defects in RNA processing might result in the neurodegenerative pathology that typifies ALS is unclear. We now present preliminary evidence suggesting that

FUS and TDP-43 are components of the cellular response to oxidative DNA damage, a process known to be important to slow or prevent neurodegeneration. We show that the FUS/TLS and TDP-43 proteins are redistributed in response to DNA damage, with FUS rapidly accumulating at sites of DNA damage and TDP-43 rapidly expelled. We show that this redistribution is an active process that is regulated by established DNA damage signalling proteins, supporting the idea that RNA processing is a bona fide component of the cellular DNA damage response. Based on these observations, we propose that RNA processing by FUS/TLS and TDP-43 is required to ensure that the stability of nascent pre-mRNA and the progression of RNA polymerase is properly managed and controlled during transcription in the presence of DNA lesions, and that mutation of these and likely other RNA processing factors results in dysfunctional gene expression at sites of DNA damage and consequently progressive neuronal cell death. We now plan to address this hypothesis directly, using a combination of molecular and cellular approaches.

Further information available at:

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