A new component of the cellular response to TOP1-induced DNA damage: the ALS protein FUS

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FUS (Fused in Sarcoma) is a nuclear RNA/DNA binding protein that plays a key role in multiple steps of RNA metabolism and the DNA Damage Response. Autosomal dominant mutations in FUS have been associated with both familial and sporadic cases of ALS (Amyotrophic lateral sclerosis), the most common adult-onset motor neuron disease, characterized by progressive degeneration of motor neurons. Of particular threat to neural maintenance and function is DNA damage induced by topoisomerases, a class of enzymes that remove torsional stress from DNA by creation of transient DNA strand break. It has been proposed that ALS mutations cause pathological changes in FUS-regulated gene expression and RNA processing, due either to loss of normal FUS function, toxic gain of function, or both. However, the nature of the endogenous sources of DNA damage that might trigger a requirement for FUS and/or other RNA-processing factors is unknown. Here, using a variety of different cell types, including human spinal motor neurons, we showed that FUS is a component of the cellular response to topoisomerase I (TOP1)-induced DNA breakage. FUS relocalised from nucleoplasm to sites of nucleolar rRNA synthesis in response to RNA polymerase II transcriptional stress induced by abortive TOP1 DNA breakage. This relocalisation was rapid and dynamic, reversing following the removal of TOP1-induced breaks and coinciding with the recovery of global transcription. The molecular role of this response is unclear, but we propose that FUS moves from sites of stalled RNA polymerase II to sites of RNA polymerase I activity either to regulate pre-mRNA synthesis and/or processing during transcriptional stress, or to modulate some yet unidentified aspect of rRNA biogenesis. Finally, we found that HeLa cells and ALS patient fibroblasts expressing mutant FUS are hypersensitive to TOP1-induced DNA breakage, highlighting the possible relevance of our findings to ALS disease pathology.