C9-ALS/FTD-linked proline–arginine dipeptide repeat protein causes neuronal cell death by associating with paraspeckle components

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A GGGGCC hexanucleotide repeat expansion in the *C9ORF72* gene has been identified as the most common genetic cause of amyotrophic lateral sclerosis and frontotemporal dementia. The repeat expansion undergoes unconventional translation to produce dipeptide repeat proteins (DPRs). Although DPRs are thought to be neurotoxic, the molecular mechanism underlying the DPR-caused neurotoxicity has not been fully elucidated. The current study shows that poly-proline-arginine (poly-PR), the most toxic DPR *in vitro*, bound to and up-regulated nuclear paraspeckle assembly transcript 1 (NEAT1) that plays an essential role as a scaffold non-coding RNA during the paraspeckle formation. The CRISPR-assisted up-regulation of endogenous NEAT1 caused neurotoxicity. We also show that the poly-PR caused neurotoxicity by modulating the function of several paraspeckle-localizing heterogeneous nuclear ribonucleoproteins. Furthermore, dysregulated expression of TAR DNA-binding protein 43 (TDP-43) up-regulated NEAT1 expression and induced neurotoxicity. These results suggest that the dysfunction of paraspeckles is linked to the poly-PR- and TDP-43-mediated neurotoxicity.