Intronic RNA as a Therapeutic Target in Neurodegeneration: A Multipronged Study of RNA Lariat Debranching Enzyme DBR1

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Neurodegeneration afflicts ~9 million, costs $800 billion/year in the US, and is one of the greatest unmet medical needs of the 21st century. Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disorder and its main driver is RNA binding protein TDP-43 aggregation. TDP-43 pathology is also observed in patients with 2 types of dementia (FTD & a subset of Alzheimer's). There is a dire urgency in elucidating the mechanisms of TDP-43 pathology and devising novel therapeutic approaches to target it. When pre-mRNA is spliced into its mature transcript, the splicing machinery cuts out the intron, resulting in the formation of an intronic lariat that is rapidly degraded by the DBR1 enzyme. Loss of DBR1 activity prevents the degradation of lariat RNA leading to its accumulation in the cell. TDP-43 aggregation/toxicity has been suggested to be ameliorated by DBR1 gene deletion. However, mechanisms behind this remain unclear. I investigated the molecular details of how lariat RNA counteracts TDP-43 aggregation/toxicity. I found that 1) Intronic lariat RNA alters the properties and toxicity of TDP-43 aggregates. 2) Lariat RNA is a general protectant against proteotoxic stress. 3) Complete loss of DBR1 has adverse effects. WT DBR1 expression cannot be knocked out/silenced, as its enzymatic role is essential, but the role of lariat RNA can be assumed via synthetic lariats. By exposing these to aggregate-prone neurons, synthetic lariats can work to modify proteotoxic stress and rescue neurodegenerative aggregate toxicity. Lariat accumulation is a conserved mechanism of how cells can armor themselves against the detrimental effects of RNA binding protein aggregation. This approach can be used to therapeutically target stress-related aggregation in neurodegeneration.