Targeting disruption of stathmin-2 in neurodegenerative diseases

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Alteration of RNA metabolism has emerged as a central theme in neurodegenerative diseases. Mutations and/or mislocalization of RNA-binding proteins, including TDP-43, have been implicated in amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), and Alzheimer’s disease. TDP-43 is involved in fundamental RNA processing activities including RNA transcription, splicing, and transport.

Recognizing the crucial role of TDP-43 in neurodegeneration, we have used genome-wide approaches to characterize how it regulates the expression and splicing of its RNA targets. We recently demonstrated that the human RNA most affected by loss of nuclear TDP-43 encodes a neuronal growth-associated factor called stathmin-2. Reduced nuclear TDP-43 results in abnormal usage of cryptic splice and polyadenylation sites in pre-mRNAs from the STMN2 gene, leading to loss of stathmin-2 protein.

Experiments in iPSC-derived TDP-43-depleted motor neurons show that stathmin-2 loss results in diminished nerve regeneration after axotomy (severing). Remarkably, although TDP-43 broadly affects the expression levels or splicing of many RNAs, restoration of stathmin-2 alone is sufficient to rescue the axonal regeneration capacity of these cells following axotomy. Stathmin-2 is also essential to maintain the axonal architecture and the connection between motor neurons and muscles. Reduced stathmin-2 level is a hallmark of sporadic and familial ALS and FTD, suggesting that restoring stathmin-2 expression is an attractive therapeutic strategy in the vast majority of patients with ALS and FTD.

We developed two approaches to block cryptic splicing of stathmin-2—one by using the CRISPR effector dCasRx and another using antisense oligonucleotides (ASOs) that bind to stathmin-2 pre-mRNA—to rescue the axonal regeneration capacity of human motor neurons with TDP-43 deficiency. We generated “humanized” stathmin-2 mice with constitutive mis-splicing of stathmin-2 and demonstrated that ASO injection into their cerebral spinal fluid rescues stathmin-2 mRNA levels. Further, we used pharmacological and genetic screens to identify modulators of stathmin-2 expression as potential novel targets for translational drug development in neurological diseases.