ALS: Altered Levels of Spliceforms in Models of Amyotrophic Lateral Sclerosis

Abstract

Amyotrophiclateral sclerosis (ALS) ts a fatal disease characterized by the progressive and rapid loss of motor neurons, resulting in paralysis and respiratory failure. Mutant forms of superoxide dismutase 1 (SOD1) ate known to be accountable for 20-250h of familial ALS cases and roughly 25 of all ALS cases, but the mechanism behind this condition remains unclear. Aberrant pre-messenger RNA splicing has been implicated in disease progression, including in exons regulated by the neuronal RNA-binding protein Nova2. To further investigate pathology and alternative splicing patterns in ALS, I employed two models. In the first, motor neurons were derived from embryonic stem cells of mice with either wildtype human SOD1 or human mutant SOD1"^{G93A} background and co-cultured with glia derived from murine cortex of either genotype. Secondly, tissue was harvested from mice transgenic fot the human SOD1^{G93A}, permitting *in vivo* studies of ALS. RNA was collected from purified cell populations or from whole tissue over a time course. mRNA sequencing (RNA-Seq) and bioinformatics analysis of these samples revealed deregulation of cassette exon expression that was tobust in symptomatic spinal cord tissue. Motor neurons expressing the mutant SOD1 protein were particularly vulnerable to cell and non-cell autonomous perturbations of splicing. A broad survey of splicing in 90 Nova2 targets weakly suggested involvement of deregulation in AIS. These observations suggest that alternative splicing events may play a role in ALS disease progression.