

CPH Seminar in Precision Medicine

“Extensive cryptic splicing upon loss of RBM17 and TDP43 in neurodegeneration models”

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Splicing regulation is an important step of post-transcriptional gene regulation. It is a highly dynamic process orchestrated by RNA-binding proteins (RBPs). RBP dysfunction and global splicing dysregulation have been implicated in many human diseases, but the *in vivo* functions of most RBPs and the splicing outcome upon their loss remain largely unexplored. Here we report that constitutive deletion of *Rbm17*, which encodes an RBP with a putative role in splicing, causes early embryonic lethality in mice and that its loss in Purkinje neurons leads to rapid degeneration. Transcriptome profiling of *Rbm17*-deficient and control neurons and subsequent splicing analyses using *CrypSplice*, a new computational method that we developed, revealed that more than half of RBM17-dependent splicing changes are cryptic. Importantly, RBM17 represses cryptic splicing of genes that likely contribute to motor coordination and cell survival. This finding prompted us to re-analyze published datasets from a recent report on TDP-43, an RBP implicated in amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), as it was demonstrated that TDP-43 represses cryptic exon splicing to promote cell survival. We uncovered a large number of TDP-43-dependent splicing defects that were not previously discovered, revealing that TDP-43 extensively regulates cryptic splicing. Moreover, we found a significant overlap in genes that undergo both RBM17- and TDP-43-dependent cryptic splicing repression, many of which are associated with survival. We propose that repression of cryptic splicing by RBPs is critical for neuronal health and survival. *CrypSplice* is available at www.liuzlab.org/CrypSplice.

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