UTHealth
The University of Texas Health Science Center at Houston
School of Biomedical Informatics

CPH Seminar in Precision Medicine

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

Zhandong Liu, Ph.D.

Assistant Professor, Computational and Integrative Biomedical Research Center at Baylor College of Medicine
Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital

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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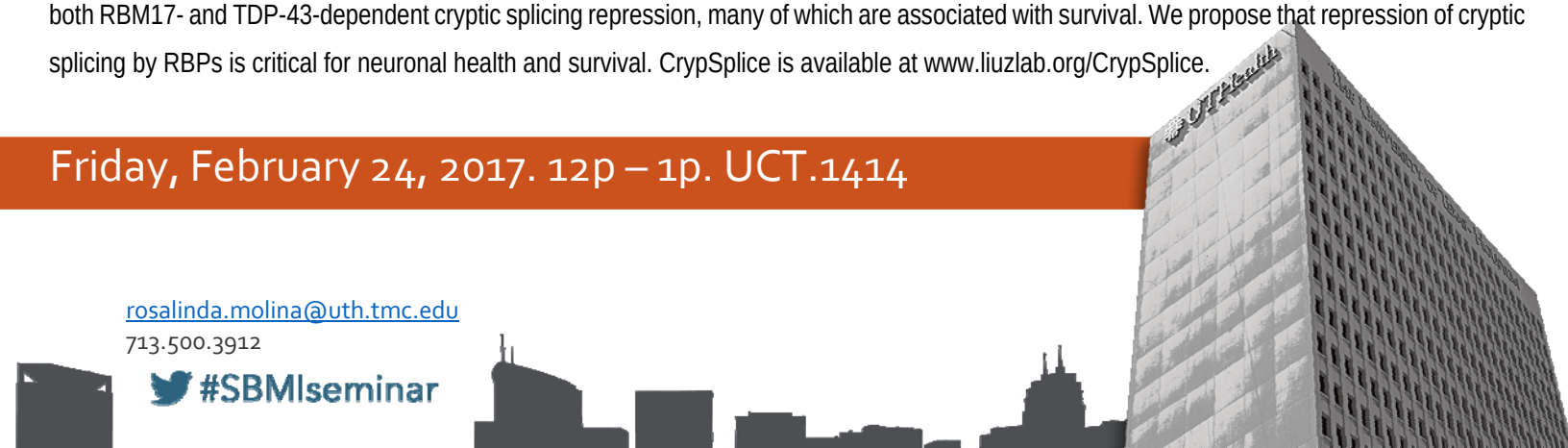

rosalinda.molina@uth.tmc.edu
713.500.3912

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