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Tip60’s Novel RNA-Binding Function Modulates Alternative Splicing of Pre-mRNA Targets Implicated in Alzheimer’s Disease

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Abstract : Context: The severity of Alzheimer’s Disease (AD) progression involves an interplay of genetics, age, and environmental factors orchestrated by histone acetyltransferase (HAT) mediated neuroepigenetic mechanisms. While disruption of Tip60 HAT action in neural gene control is implicated in AD, alternative mechanisms underlying Tip60 function remain unexplored. Altered RNA splicing has recently been highlighted as a widespread hallmark in the AD transcriptome that is implicated in the disease. Research Aim: The aim of this study was to identify a novel RNA binding/splicing function for Tip60 in human hippocampus and impaired in brains from AD fly models and AD patients. Methodology/Analysis: The authors used RNA immunoprecipitation using RNA isolated from 200 pooled wild type Drosophila brains for each of the 3 biological replicates. To identify Tip60’s RNA targets, they performed genome sequencing (DNB-SequencingTM technology, BGI genomics) on 3 replicates for Input RNA and RNA IPs by Tip60. Findings: The authors' transcriptomic analysis of RNA bound to Tip60 by Tip60-RNA immunoprecipitation (RIP) revealed Tip60 RNA targets enriched for critical neuronal processes implicated in AD. Remarkably, 79% of Tip60’s RNA targets overlap with its chromatin gene targets, supporting a model by which Tip60 orchestrates bi-level transcriptional regulation at both the chromatin and RNA level, a function unprecedented for any HAT to date. Since RNA splicing occurs co-transcriptionally and splicing defects are implicated in AD, the authors investigated whether Tip60-RNA targeting modulates splicing decisions and if this function is altered in AD. Replicate multivariate analysis of transcript splicing (rMATS) analysis of RNA-Seq data sets from wild-type and AD fly brains revealed a multitude of mammalian-like AS defects. Strikingly, over half of these altered RNAs were bonafide Tip60-RNA targets enriched for in the AD-gene curated database, with some AS alterations prevented against by increasing Tip60 in fly brain. Importantly, human orthologs of several Tip60-modulated spliced genes in Drosophila are well characterized aberrantly spliced genes in human AD brains, implicating disruption of Tip60’s splicing function in AD pathogenesis. Theoretical Importance: The authors' findings support a novel RNA interaction and splicing regulatory function for Tip60 that may underlie AS impairments that hallmark AD etiology. Data Collection: The authors collected data from RNA immunoprecipitation experiments using RNA isolated from 200 pooled wild type Drosophila brains for each of the 3 biological replicates. They also performed genome sequencing (DNBSequencingTM technology, BGI genomics) on 3 replicates for Input RNA and RNA IPs by Tip60. Questions: The question addressed by this study was whether Tip60 has a novel RNA binding/splicing function in human hippocampus and whether this function is impaired in brains from AD fly models and AD patients. Conclusions: The authors' findings support a novel RNA interaction and splicing regulatory function for Tip60 that may underlie AS impairments that hallmark AD etiology.

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