Engineering DYRK1A overdosage yields Down syndrome-characteristic cortical splicing aberrations

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Created 12/4/2011
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Abstract:

Down syndrome (DS) associates with impaired brain functions, but the underlying mechanism(s) are yet unclear. The "gene dosage" hypothesis predicts that in DS, overexpression of a single gene can impair multiple brain functions through a signal amplification effect due to impaired regulatory mechanism(s). Here, we report findings attributing to impairments in the splicing process such a regulatory role. We have used DS fetal brain samples in search for initial evidence and employed engineered mice with MMU16 partial trisomy (Ts65Dn) or direct excess of the splicing-associated nuclear kinase Dyrk1A, overdosed in DS for further analyses. We present specific albeit modest changes in the DS brain's splicing machinery with subsequently amplified effects in target transcripts; and we demonstrate that engineered excess of Dyrk1A can largely recapitulate these changes. Specifically, in both the fetal DS brains and the Dyrk1A overdose models, we found ample modestly modified splicing-associated transcripts which apparently induced secondary enhancement in exon inclusion of key synaptic transcripts. Thus, DS-reduced levels of the dominant-negative TRKBT1 transcript, but not other TRKB mRNA transcripts, were accompanied by corresponding decreases in BDNF. In addition, the DS brains and Dyrk1A overdose models showed selective changes in the transcripts composition of neuroligin mRNAs as well as reductions in the "synaptic" acetylcholinesterase variant AChE-S mRNA and corresponding increases in the stress-inducible AChE-R mRNA variant, yielding key synaptic proteins with unusual features. In cotransfected cells, Dyrk1A overdosage caused parallel changes in the splicing pattern of an AChE mini-gene, suggesting that Dyrk1A overdosage is both essential and sufficient to induce the observed change in the composition of AChE mRNA variants. Furthermore, the Dyrk1A overdosage animal models showed pronounced changes in the structure of neuronal nuclear speckles, where splicing events take place and in SR proteins phosphorylation known to be required for the splicing process. Together, our findings demonstrate DS-like brain splicing machinery malfunctioning in Dyrk1A overexpressing mice. Since individual splicing choices may alter cell fate determination, axon guidance, and synaptogenesis, these findings suggest the retrieval of balanced splicing as a goal for DS therapeutic manipulations early in DS development.

Journal: Neurobiol Dis

Volume: 40
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