Reprogramming of tau alternative splicing by spliceosome-mediated RNA trans-splicing: implications for tauopathies. [1]

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Abstract	Frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17) is caused by mutations in the gene encoding the microtubule-associated protein, tau. Some FTDP-17 mutations affect exon 10 splicing. To correct aberrant exon 10 splicing while retaining endogenous transcriptional control, we evaluated the feasibility of using spliceosome-mediated RNA trans-splicing (SMaRT) to reprogram tau mRNA. We designed a pre-trans-splicing molecule containing human tau exons 10 to 13 and a binding domain complementary to the 3' end of tau intron 9. A minigene comprising tau exons 9, 10, and 11 and minimal flanking intronic sequences was used as a target. RT-PCR analysis of SH-SY5Y cells or COS cells cotransfected with a minigene and a pre-trans-splicing molecule using primers to opposite sides of the predicted splice junction generated products containing exons 9 to 13. Sequencing of the chimeric products showed that an exact exon 9-exon 10 junction had been created, thus demonstrating that tau RNA can be reprogrammed by trans-splicing. Furthermore, by using the same paradigm with a minigene containing full-length intronic sequences, we show that cis-splicing exclusion of exon 10 can be by-passed by trans-splicing and that conversion of exon 10(-) tau RNA into exon 10(+) tau RNA could be achieved with approximately 34% efficiency. Our results demonstrate that an alternatively spliced exon can be replaced by trans-splicing and open the way to novel therapeutic applications of SMaRT for tauopathies and other disorders linked to aberrant alternative splicing.
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