EXAMINE THE ROLE OF MINOR SPLICING PATHWAY
IN SPINAL MUSCULAR ATROPHY

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ABSTRACT

Spinal Muscular Atrophy is an autosomal recessive disorder mainly caused by deletions or mutations of one gene, Survival Motor Neuron (SMN). SMN is crucial in snRNP assembly for splicing pathways. Previous studies showed a significant decrease in the levels of minor splicing (U12 intron) snRNPs in SMA mice and a restoration of a U12 intron-containing gene partially rescued disease phenotypes in SMA animal models. Here we utilized a self-complementary adeno-associated virus serotype9 (scAAV9) to investigate the potential effect of increasing minor splicing snRNAs on SMN deficiency. We introduced minor splicing snRNAs, human U11 and U12, or human U11, U12 with U4atac to the well-characterized SMNΔ7 model. Our treatment prolonged survival and increased percent peak weight gain. The motor function was improved however NMJ pathology was largely uncorrected. Nonetheless, the increment of minor splicing snRNAs maintained the number of central synapses on motor neurons. Furthermore, no changes in SMN expression after the treatment indicated that increasing minor splicing snRNAs partially benefits disease phenotypes independent to SMN expression in SMA mice. Furthermore, defects in U12-intron splicing events were partially corrected for U12 intron-containing SMN target gene, *Stasimon*, reiterating the improvement of minor splicing in SMA mice. Taken together, our results showed the restoration of minor splicing snRNAs partially ameliorates SMN deficiency caused phenotypes, indicating that U12-dependent minor splicing event is responsible for the disease progress of SMA.