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Title: Investigating differential intron sensitivity to core spliceosome factors that are amplified or deleted in developmental syndromes and cancer

Abstract

Our genome contains around 20,000 protein-coding genes; however, through alternative splicing, a vastly larger number of mRNA isoforms is produced. In addition to increasing unique protein-coding isoforms, splicing can affect gene expression through nonsense-mediated decay (NMD) or intron detention. The splicing machinery is large and highly dynamic, composed of more than 150 proteins and RNAs, recruited in a stepwise manner. The U2 snRNP is responsible for positioning the 3' splice site, and SF3B1, the largest protein subunit of the SF3B subcomplex of the U2 snRNP, acts as a hub that can coordinate with many splicing factors to enable U2 snRNP to recognize the correct branch point and ensure the appropriate structural rearrangements occur to facilitate splicing. SF3B1 mutations occur in different cancer subtypes at specific hotspots mapped to HEAT repeats in the C-terminus that can cause a 3' splice site shift, or other splicing alterations, including detained intron splicing. Intriguingly, some of the splicing factors that interact directly with SF3B1, like PUF60, U2AF65, and SF3B4, are amplified in cancers and deleted in developmental syndromes like Verheij and Nager/Rodriguez syndromes. In order to understand how overexpression or depletion of these disease-associated splicing factors affects global splicing patterns, I will employ the CRISPRa/I systems, which allow specific genes to undergo targeted transcriptional up- or down-regulation. With this approach, we can compare the effects of higher or lower than normal expression of these key splicing factors and potentially gain insight into the causative events for these diseases caused by splicing dysregulation.