

MOLECULAR TARGETS AND CANCER THERAPEUTICS

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Multigenomic characterization of context-dependent alternative splicing in normal and neoplastic cells

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Abstract: Alternative pre-mRNA splicing (AS) supports the dynamic and regulated diversification of cells by allowing the production of multiple distinct proteins from individual genes. Dysregulated AS is commonly associated with human malignancies, producing pathological proteomes that underpin disease initiation, progression, and emergence of therapy resistance. The CDC2-like kinases (CLKs) and dual-specificity tyrosine-regulated kinases (DYRKs) are thought to govern the efficiency and specificity of AS by directly phosphorylating serine/arginine-rich splicing factors (SRSFs) and thereby influencing pre-mRNA splice junction selection. Cirtuvivint (SM08502) is a first-in-class small molecule ATP-competitive inhibitor of CLK/DYRK kinases. To directly evaluate the contribution of these kinases to AS profiles, changes in AS following treatment with cirtuvivint followed by high-depth RNAseq analysis across 19 cell lines representing 6 tumor lineages were evaluated. Both baseline and drug-induced changes in AS events (ASEs) were measured using a multivariate analysis of transcript splicing (rMATS). Pan-CLK/DYRK inhibition was found to affect a minority of baseline ASEs, leaving the majority of spliceosome activity intact in all samples. However, the magnitude and quantity of detected drug-induced alterations were larger in a sample of tumor cells from a patient compared with adjacent non-tumorigenic cells. Moreover, most ASEs sensitive to pan-CLK/DYRK inhibition were tumor type-specific irrespective of selective presence at the gene level. Multi-omics data integration revealed sensitivity to cirtuvivint was associated with alterations in splicing genes and that drug-induced ASEs were significantly associated with disease-promoting biology across lineage and oncogenic driver contexts. Perturbed splicing of the AR-V7 variant in treatment-resistant prostate cancer and MDM2 in p53 wild-type cancers were prominent examples. These observations indicate vulnerabilities to CLK-DYRK regulated splicing span a wide range of oncogenic contexts with potential to be therapeutically addressed with pan CLK/DYRK inhibitors.