RNA splicing factor (SF) mutations are common in leukemias and increase susceptibility to perturbations in splicing, spurring attempts to develop treatments that inhibit the spliceosome. Fong and colleagues developed a list of druggable target proteins likely to interact with the spliceosome, then performed a drug screen using a mouse cell line modeling human acute myeloid leukemia with a mutation in spliceosome component SRSF2. The screen identified several drugs that were more lethal to Srsf2-mutant cells than to wild-type Srsf2 (Srsf2WT) controls, including inhibitors of components of the extended splicing network; specifically, protein arginine methyltransferase (PRMT) inhibitors emerged as being preferentially lethal to Srsf2-mutant AML cells, which had tenfold higher sensitivity to a selective PRMT5 inhibitor and a pan-type I PRMT inhibitor. Treatment with a PRMT5 inhibitor led to increased survival in mice with Srsf2-mutant tumors but not in mice with Srsf2WT tumors, and spleens from mice treated with the drug exhibited reduced levels of symmetrical dimethylarginine. Likewise, mice with Srsf2-mutant but not Srsf2WT leukemias exhibited delayed disease progression when treated with a pan-type I PRMT inhibitor.


Minor Finding: Splicing factor mutations increased protein arginine methyltransferase (PRMT) inhibitor sensitivity.

Concept: Combined treatment with inhibitors of PRMT5 and pan-type I PRMTs caused synergistic effects.

Impact: It may be worthwhile to screen patients in PRMT-inhibitor trials for splicing-factor mutations.

CANCER-LINKED SF3B1 MUTATIONS CAUSE FAULTY SPLICING AND SUGP1 BINDING

Mutations in the gene encoding splicing factor 3b subunit 1 (SF3B1) are commonly found in patients with myelodysplastic syndromes (MDS) and several other cancers, such as chronic lymphocytic leukemia, uveal melanoma, and breast cancer. In an analysis of 15 patients with MDS (six with different SF3B1 mutations; nine without), Zhang and colleagues discovered that SF3B1 mutations were associated with abnormal 3′ splice site (3′ ss) usage. Overexpression of one of the mutant SF3B1 variants in a human cell line corroborated the notion that the mutation itself was responsible for the use of cryptic 3′ ss. In myelogenous leukemia cells, expression of SF3B1K700E (the most common mutant protein expressed in patients with MDS) led to the formation of aberrant spliceosomes lacking a normal proportion of the protein SUGP1. Further implying that the selection of cryptic 3′ ss was due to a reduced interaction between SF3B1 and SUGP1, yielding spliceosomes lacking SUGP1, loss of SUGP1 caused the same phenotype that expression of SF3B1K700E did, as did expression of a dominant-negative SUGP1 mutant. Overexpression of SUGP1 in SF3B1K700E-expressing cells increased association between SUGP1 and mutant SF3B1 complexes and partially rescued the splicing errors caused by the mutation in SF3B1, implying that loss of SUGP1 from the spliceosome complex is responsible for the splicing defects caused by SF3B1 mutation. Indicating the broader relevance of these findings, expression of four other mutant versions of SF3B1 commonly found in cancers also decreased SUGP1’s association with SF3B1 and resulted in abnormal selection of 3′ ss. These findings outline a possible mechanistic explanation for the observed association of SF3B1 mutations with cancers and provide insight that may be drawn upon for future drug development.


Major Finding: SF3B1 mutations, common in myelodysplastic syndromes, cause SUGP1-mediated splicing defects.

Mechanism: SUGP1 fails to associate with SF3B1-mutant spliceosomes, leading to aberrant 3′ splice site selection.

Impact: Mechanistic understanding of the impact of SF3B1 mutations may provide hints for drug development.
Splicing Factor-Mutant Leukemias Are Sensitive to PRMT Inhibitors

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