Splicing

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.

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 $SF3B1^{K700E}$ (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 $SF3B1^{K700E}$ did, as did expression of a dominant-negative SUGP1 mutant. Overexpression of SUGP1 in $SF3B1^{K700E}$-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. ■

Zhang J, Ali AM, Lieu YK, Liu Z, Gao J, Rabadan R, et al. Disease-causing mutations in SF3B1 alter splicing by disrupting interaction with SUGP1. Mol Cell 2019 Aug 29 [Epub ahead of print].

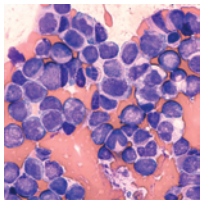
Leukemia

Major 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.

SPLICING FACTOR-MUTANT LEUKEMIAS ARE SENSITIVE TO PRMT INHIBITORS



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* ($Srsf2^{WT}$) 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 $Srsf2^{WT}$ tumors, and spleens from mice treated with the drug exhibited reduced levels of symmetrical dimethylarginine. Likewise, mice with *Srsf2*-mutant but not $Srsf2^{WT}$ leukemias exhibited delayed disease progression when treated with a pan-type I PRMT inhibitor. Experiments using mouse leukemia cell lines, human leukemia cell lines, induced pluripotent stem cells differentiated into hematopoietic progenitor cells, and patient-derived xenograft mouse models all pointed to synergy between drugs targeting different aspects of splicing catalysis, and this effect was increased in the presence of mutations in SFs; experiments in human leukemia cell lines revealed that the synergistic drug effects also extended to changes in alternative splicing. PRMT5 and type I PRMTs methylated distinct groups of proteins, and genes involved in mitosis and the cell cycle were upregulated in both $SRSF2^{WT}$ and *SRSF2*-mutant cells treated with inhibitors of PRMT5, pan-type I PRMT inhibitors, or a combination of the two. Further, there was a decrease in cells in G1 and S phase and an increase in an apoptotic sub-G1 population of cells. These results suggest that mutations in splicing factors should be considered in trials of PRMT5 and type I PRMT inhibitors. ■

Fong JY, Pignata L, Goy P, Kawabata KC, Lee SC, Koh CM, et al. Therapeutic targeting of RNA splicing catalysis through inhibition of protein arginine methylation. Cancer Cell 2019;36:194–209.E9.