Spliceosomal Gene Mutations in Cancer

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Somatic mutations in genes encoding components of the spliceosome have been identified in a spectrum of human malignancies, including ~60% of patients with myelodysplastic syndromes (MDS). These mutations occur most commonly in *SF3B1*, *SRSF2*, and *U2AF1* and almost always as heterozygous missense mutations that are mutually exclusive, suggesting that they confer an alteration of splicing function and/or that cells may only tolerate a certain degree of splicing modulation. We recently identified that mice expressing the heterozygous *Srsf2*P95H mutation develop MDS-like features due to altered RNA binding and splicing preference of the mutant protein. These biological and mechanistic features of the mutant SRSF2 protein are distinct from those seen with loss of 1 or copies of SRSF2, indicating that SRSF2 mutations confer an alteration of function. Specifically, mutations in SRSF2 alter its binding to exonic splicing enhancers (ESEs) such that the mutant protein recognize C-rich ESE sequences over G-rich ESEs whereas the wildtype protein recognizes C-and G-rich ESEs similarly.

While the above data suggest that mutations in spliceosomal proteins confer an alteration of function, it is still unclear why these mutations are heterozygous or why they are mutually exclusive with one another. In order to address these questions, we performed series of murine genetic experiments to study the effect of (1) loss of the wildtype allele while concomitantly expressing a mutant splicing factor and (2) expressing 2 mutant splicing splicing factors within the same cell concomitantly. Overall, our murine genetic experiments suggest that cells bearing spliceosomal mutations do not tolerate additional perturbations to splicing function. We next tested whether spliceosome-mutant leukemias display greater sensitivity to pharmacologic splicing inhibition induced by the small molecule E7107. Treatment of isogenic murine leukemias as well as patient-derived xenograft (PDX) AMLs showed significant reductions in leukemic burden specifically in samples carrying spliceosomal mutations. Collectively, these data provide genetic and pharmacologic evidence that leukemias with spliceosomal mutations are preferentially susceptible to additional splicing perturbations *in vivo* compared with wildtype counterparts. Modulation of spliceosome function may provide a novel therapeutic avenue in genetically defined subsets of MDS/AML patients.