SPLICEOSOMAL-RNA MUTATIONS MAY DRIVE MEDULLOBLASTOMA AND OTHER CANCERS

Mutations that cause genome-wide missplicing have recently been established to drive pathogenesis in some cancer types, but most spliceosomal mutations that have been characterized are in protein subunits of the spliceosome, whereas the spliceosome’s RNA components have been understudied in comparison. In several cancer types, Shuai, Suzuki, Navarro, and colleagues found evidence of recurrent A-to-C and A-to-G mutations at the third nucleotide of U1 snRNA, a spliceosome component. U1 uses base pairing to recognize the 5′ splice site; thus, this mutation causes normal 5′ splice sites to be missed and creates aberrant splice junctions, including in recognized cancer drivers. These results provide evidence for a previously unknown mechanism by which splicing defects may promote cancer development. Notably, the group discovered that U1-hotspot mutations occurred with high frequency in medulloblastoma, a finding that was further investigated by Suzuki, Kumar, and colleagues. Their study revealed that hotspot mutations at the third nucleotide of U1 are present in 97% of tumors from adult patients with Sonic Hedgehog medulloblastoma (SHH-MB), 25% of tumors from adolescent patients with SHH-MB, and essentially no tumors from infant patients with SHH-MB; the mutation was also absent in tumors from patients with other medulloblastoma subtypes. Interestingly, the A-to-G mutation occurred in 10% of patients with the aggressive subtype of chronic lymphocytic leukemia, a disease that lies on the other end of the age spectrum compared with medulloblastoma. Further analysis demonstrated that adolescent patients with SHH-MB who had U1-hotspot mutations and TP53 mutations had significantly worse prognoses than those without the mutations, suggesting that prioritizing this patient group for targeted therapies may be warranted. Together, these two studies illustrate the potential value of broadening the range of genomic regions explored when searching for cancer drivers.

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Major Finding: Hotspot mutations in U1 snRNA are associated with several cancers and cause aberrant splicing.

Concept: These mutations are common in adult (97%) and adolescent (25%) Sonic Hedgehog medulloblastoma.

Impact: These studies establish a link between U1-hotspot mutations and cancer, especially medulloblastoma.

Breast Cancer

Major Finding: The novel CDK12/13 inhibitor SR-4835 was effective in mouse models of triple-negative breast cancer.

Concept: SR-4835 is highly selective for CDK12/13 and synergizes with DNA-damaging agents.

Impact: Continued investigation of SR-4835 in triple-negative breast cancer is warranted.

CDK12/13 INHIBITOR SR-4835 IS ACTIVE IN TRIPLE-NEGATIVE BREAST CANCER

Some triple-negative breast cancers (TNBC) with mutations affecting homologous recombination, such as mutations in BRCA1, are sensitive to treatment with poly(ADP-ribose) polymerase (PARP) inhibitors and platinum-based chemotherapies; however, relapse is common with advanced disease. Quereda and colleagues report the development of the orally bioavailable CDK12/13 inhibitor SR-4835, an agent that may have potential for treatment of TNBC. The compound was developed using structure-guided optimization based on the most selective known inhibitor of CDK12/13, and biochemical assays using a panel of more than 450 kinases demonstrated that SR-4835 is highly selective for CDK12/13, with a half-maximal effective concentration of 100 nM. Further, TNBC cell lines exhibited sensitivity to low-nanomolar concentrations of the drug, and treatment resulted in an increase in DNA damage and apoptosis. Genetic inactivation of CDK12 or CDK13 resulted in a similar phenotype. RNA-sequencing experiments using cells treated with SR-4835 demonstrated that the drug caused downregulation of genes involved in DNA repair and recombination and upregulation of genes involved in cell-cycle progression and apoptosis. Accordingly, SR-4835 synergized with DNA-damaging agents and PARP inhibitors to inhibit cancer cell growth. Experiments using a patient-derived xenograft (PDX) model of TNBC showed that treatment with cisplatin or SR-4835 decreased tumor growth, and combination treatment with SR-4835 and cisplatin resulted in rapid tumor regression without apparent gross toxicity. In a second PDX model, similar results were observed following combination treatment with SR-4835 and irinotecan. Collectively, these findings suggest that SR-4835 is a promising early-stage drug worthy of further investigation in TNBC.

CDK12/13 Inhibitor SR-4835 Is Active in Triple-Negative Breast Cancer

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