

Perturbation of RNA splicing fidelity hampers pancreatic cancer cell viability by disrupting DNA repair proficiency and mitotic checkpoint integrity

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Background: Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive cancer with a remarkably poor prognosis. Splicing dysregulation is emerging as a hallmark of cancer, influencing multiple aspects of tumor development, including PDAC.

Methods: To evaluate the impact of splicing dysregulation in PDAC we analyze the effect of splicing-targeting drugs Pladienolide B, Thailanstatin A and Indisulam in PDAC cell lines and PDOs. RNA sequencing was performed to identify the genome-wide effects of splicing inhibition on the transcriptome of PDAC cells and PDOs. Viability assays and cell cycle analysis with PDAC models were performed to assess the efficacy of splicing-targeting drugs as single agent or in combination with clinically relevant drugs.

Results: Transcriptome analyses revealed that splicing inhibition negatively affects the DDR pathway (BRCA1, CHEK1, CHEK2) in homologous recombination-proficient (HRP) PDAC models, enhancing sensitivity to Talazoparib treatment. Moreover, splicing-targeting drugs impair splicing of mitotic checkpoint genes (AURKA, AURKB, CDC25B, EZH2), leading to severe mitotic defects with a strong enrichment in the G2/M phase of the cycle and formation of multinucleated cells. Combined treatments with AZD7762 and Alisertib have an additive effect on PDAC models' viability.

Conclusion: Splicing inhibition impairs DDR pathway in HRP PDAC models and represents an efficacious strategy to sensitize these tumors to treatment with PARPi. Moreover, our findings imply that PDAC cells are dependent on efficient splicing for proper execution of mitosis suggesting that drugs targeting mitotic proteins may represent a valuable therapeutic approach in PDAC.