Big Data Training for Cancer Research

Special Lecture Series

Role of RNA helicase DDX5 in Hepatitis B Virus hepatocellular carcinoma and treatment

Dr. Ourania Andrisani

May 25, 2023, 1:00 – 2:15 PM (EDT)

Abstract: Reduced expression of RNA helicase DDX5 associates with increased hepatocellular carcinoma (HCC) grade, and poor patient survival following treatment with sorafenib. Although immunotherapy is first-line treatment, sorafenib/multi-tyrosine kinase inhibitors (mTKIs) are widely used in HCC patients when immunotherapy is contra-indicated or has failed. Sorafenib/mTKIs downregulated DDX5 in vitro and preclinical HCC models; interestingly, DDX5 overexpression reduced viability of sorafenib-treated cells via ferroptosis, suggesting a role for DDX5 in sorafenib sensitivity. RNAseq of wild-type vs. DDX5-knockdown cells treated with or without sorafenib, identified common genes repressed by DDX5 and upregulated by sorafenib. These genes significantly overlap the Wnt/β-catenin and non-canonical NF-κB pathways, including Dishevelled 1 (DVL1) and non-canonical NF-κB-inducing kinase (NIK), which are key regulators of the respective pathways. We found that DDX5 downregulation activated Wnt signaling by de-repressing DVL1 transcription; in turn, Wnt activation induced NIK transcription and non-canonical NF-κB signaling activation. These pathways converge to rescue sorafenib-treated cells from ferroptosis by inducing the transcription of NRF2, a key transcription factor for anti-ferroptotic/cytoprotective genes. Based on these findings, in vivo siRNA-mediated knockdown of NRF2 or β-catenin, a key mediator of Wnt signaling, employing the novel Nanosac-encapsulated siRNA carrier, or overexpression of DDX5 significantly reduced tumor growth, improving the antitumor efficacy of sorafenib in HCC xenograft models. We conclude, DDX5 downregulation by sorafenib confers resistance via NRF2 expression and ferroptosis escape. DDX5 restoration enhances the antitumor efficacy of sorafenib in preclinical models and can be explored as a novel therapeutic strategy for the treatment of liver cancer.

Speaker Bio: Dr. Andrisani's research interests and expertise are on molecular mechanisms of transcriptional regulation, epigenetics, and signal transduction involved in cell growth control, cellular differentiation and cancer pathogenesis. Her laboratory studies epigenetic mechanisms involved in Hepatitis B virus (HBV) biosynthesis and virus-mediated hepatocarcinogenesis. The goal is to identify essential mechanisms, which can serve as therapeutic targets, to suppress both HBV infection and the resulting HBV-mediated liver cancer. One such mechanism involves the RNA helicase DDX5, which stabilizes the epigenetic Polycomb Repressive Complex 2 (PRC2); downregulation of DDX5 is advantageous for HBV replication, and also associates with poor prognosis liver cancer. Her recent study has also demonstrated that the DDX5 controls the translation of the transcription factor STAT1, by resolving a G-quadruplex structure at the 5'UTR of STAT1 mRNA. STAT1 is essential in all types of Interferon signaling. Moreover, the family of DEAD/H box RNA helicases has attracted the interest of NIH, regarding their roles in health and disease, evidenced by a workshop she co-organized with Dr. M. Gale on this topic. For a complete listing of Dr. Andrisani's publications, please visit https://www.ncbi.nlm.nih.gov/myncbi/1-OUdGRL_yVA1/bibliography/public/.

Please click the following link to join the webinar: https://purdue-edu.zoom.us/j/95118072973