BIO_08 - Regulation of the epigenetic machinery in pancreatic cancer

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Introduction: There aren't biomarkers defined for pancreatic adenocarcinoma (PDAC). Recently, long non- coding RNAs (lncRNAs) have been assessed as potential biomarkers. lncRNAs don't code to proteins. These transcripts can guide chromatin remodeling enzymes to specific *locus* or acting as decoy. EZH2 catalyzes the methylation of histone 3 at lysine 27. EZH2 can also activate genes by other means. LncRNAs can recruit EZH2 to silence a tumor suppressor or activate an oncogene. Distinct methylation profiles arise from lncRNAs misregulation in cancer and differential EZH2 recruitment, which can lead to chemoresistance.

Objectives: Identify lncRNAs interacting with EZH2. Assess the expression of lncRNAs and protein-coding genes contrasting naïve and chemoresistant pancreatic adenocarcinoma cells.

Methodology: Systematic review of the literature found hundreds of lncRNAs that are associated with response to therapies. The lists of lncRNAs that interact with EZH2 and EZH2 targets were used to find candidates of interest. Real time PCR and RNA immunoprecipitation (RIP) experiments were employed with parental and gemcitabine-resistant cells derived from PDAC cell line AsPC-1. RIPs detected the interaction of lncRNAs and EZH2, which may result in regulation of chemoresistance-associated genes. The nuclear fraction of AsPC-1 was incubated with an antibody for EZH2, later precipitated with magnetic beads. The RNAs attached to the EZH2- antibody-beads complex were isolated. Reverse transcription and qPCR allowed the detection of lncRNAs.

Results: Among the lncRNAs reported interacting with EZH2 in PDAC, 3 were associated with response to gemcitabine. There was a differential enrichment of interacting lncRNAs among naïve and chemoresistant cell lines. HOTTIP and PVT1 were detected in chemoresistant PDAC for the first time. This suggests a mechanism seen in the HOTTIP- or PVT1-mediated chemoresistance in other cancers. LINC01133 was observed in a chemoresistant cancer for the first time. Other lncRNAs have never been reported interacting with EZH2 in any context.

Conclusion: LncRNAs guide EZH2 to regulate chemoresistance-associated genes. Combinatorial therapies targeting both EZH2 and the lncRNAs guiding it might be the key to overcoming chemoresistance in several cancers.

Keywords: epigenetics, lncRNAs, chemoresistance