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The Regulation of the Cancer Epigenetic Landscape Lies in the Realm of the Long Non-coding RNAs

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Abstract : Pancreatic adenocarcinoma (PDAC) patients have a less than 10% 5-year survival rate. PDAC has no defined diagnostic and prognostic biomarkers. Gemcitabine is the first-line drug in PDAC and several other cancers. Long non-coding RNAs (lncRNAs) contribute to the tumorigenesis and are potential biomarkers for PDAC. Although lncRNAs aren't translated into proteins, they have important functions. LncRNAs can decoy or recruit proteins from the epigenetic machinery, act as microRNA sponges, participate in protein translocation through different cellular compartments, and even promote chemoresistance. The chromatin remodeling enzyme EZH2 is a histone methyltransferase that catalyzes the methylation of histone 3 at lysine 27, silencing local expression. EZH2 is ambivalent, it can also activate gene expression independently of its histone methyltransferase activity. EZH2 is overexpressed in several cancers and interacts with lncRNAs, being recruited to a specific locus. EZH2 can be recruited to activate an oncogene or silence a tumor suppressor. The lncRNAs misregulation in cancer can result in the differential recruitment of EZH2 and in a distinct epigenetic landscape, promoting chemoresistance. The relevance of the EZH2-lncRNAs interaction to chemoresistant PDAC was assessed by Real Time quantitative PCR (RT-qPCR) and RNA Immunoprecipitation (RIP) experiments with naïve and gemcitabine-resistant PDAC cells. The expression of several lncRNAs and EZH2 gene targets was evaluated contrasting naïve and resistant cells. Selection of candidate genes was made by bioinformatic analysis and literature curation. Indeed, the resistant cell line showed higher expression of chemoresistant-associated lncRNAs and protein coding genes. RIP detected lncRNAs interacting with EZH2 with varying intensity levels in the cell lines. During RIP, the nuclear fraction of the cells was incubated with an antibody for EZH2 and with magnetic beads. The RNA precipitated with the beads-antibody-EZH2 complex was isolated and reverse transcribed. The presence of candidate lncRNAs was detected by RT-qPCR, and the enrichment was calculated relative to INPUT (total lysate control sample collected before RIP). The enrichment levels varied across the several lncRNAs and cell lines. The EZH2-lncRNA interaction might be responsible for the regulation of chemoresistance-associated genes in multiple cancers. The relevance of the lncRNA-EZH2 interaction to PDAC was assessed by siRNA knockdown of a lncRNA, followed by the analysis of the EZH2 target expression by RT-qPCR. The chromatin immunoprecipitation (ChIP) of EZH2 and H3K27me3 followed by RT-qPCR with primers for EZH2 targets also assess the specificity of the EZH2 recruitment by the lncRNA. This is the first report of the interaction of EZH2 and lncRNAs HOTTIP and PVT1 in chemoresistant PDAC. HOTTIP and PVT1 were described as promoting chemoresistance in several cancers, but the role of EZH2 is not clarified. For the first time, the lncRNA LINC01133 was detected in a chemoresistant cancer. The interaction of EZH2 with LINC02577, LINC00920, LINC00941, and LINC01559 have never been reported in any context. The novel lncRNAs-EZH2 interactions regulate chemoresistant-associated genes in PDAC and might be relevant to other cancers. Therapies targeting EZH2 alone weren't successful, and a combinatorial approach also targeting the lncRNAs interacting with it might be key to overcome chemoresistance in several cancers.

Keywords : epigenetics, chemoresistance, long non-coding RNAs, pancreatic cancer, histone modification
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