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Up-Regulation of the RNA-Binding Proteins SAM68 and PTB Contributes to the Acquisition of a Drug-Resistance Phenotype in Pancreatic Adenocarcinoma Cells

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Context The limited effect of conventional chemotherapy in pancreatic adenocarcinoma (PDAC) urges for novel therapies, targeting more directly the molecular aberrations of this disease. The molecular characterization of the drug resistant phenotype of PDAC cells remain largely unexplored, even though some evidence suggests a correlation with the expression of mesenchymal markers. Notably, the epithelial-to-mesenchymal transition (EMT) is promoted by finely-tuned changes in gene expression, occurring at both transcriptional and splicing levels. In this regard, recent observations have shown the requirement for select splicing factors during EMT. **Objective** Characterization of the molecular events leading to drug resistance in PDAC cells. **Methods** Chronic exposure to gemcitabine to select drug-resistant PDAC cell subpopulations. Western blot analyses for the expression of cancer related proteins, RNA-interference of selected genes to investigate their function. Trypan blue cell count, immuno-fluorescence analysis of the cleaved of caspase-3 and clonogenic assay to analyze cell survival. PCR analysis to detect EMT markers and immuno-fluorescence analysis of phalloidin to detect actin cytoskeleton morphology. Scratch assay to test cell migration. **Results** The chronic exposure of PDAC cells to gemcitabine selected a subpopulation of cells that displays a mesenchymal phenotype and is less sensitive to drug-induced cell death. These cells express higher levels of SAM68 and PTB, two splicing factors with oncogenic functions in other types of human cancers. Depletion of SAM68 and PTB expression caused a partial recovery of drug sensitivity, suggesting that they contribute to the acquisition of the drug-resistant phenotype. **Conclusion** Our data indicate that SAM68 and PTB may represent suitable molecular targets to counteract the drug resistance of PDAC cells.