NEXTFRONTIERS TOCURECANCER2022
DE 22 A 25/06 - 100% ONLINE

A.C.Camargo Cancer Center
Especializado em Vida

Identification of long noncoding RNAs involved in the cancer stem phenotype in pancreatic cancer

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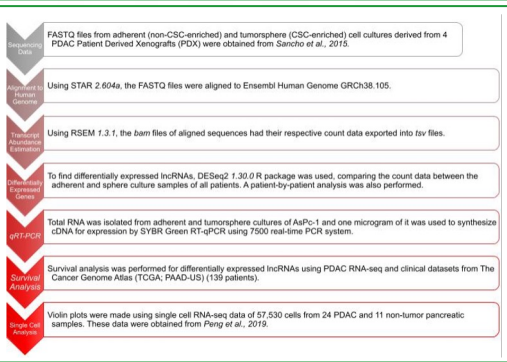
Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal disease characterized by aggressive metastatic dissemination. One of the most important hallmarks of metastatic capability is the acquisition and maintenance of a stem-like phenotype by cancer stem cells (CSCs), a process that is still poorly understood in PDAC. Nonetheless, there are already indications that it is a process that does not depend on additional mutations in the genome, but on epigenetic regulatory mechanisms. Therefore, due to their known involvement in epigenetic regulation, we hypothesize that long non-coding RNAs (lncRNAs) are important players in the acquisition of the stem-like phenotype in PDAC.

Aims

Considering that acquisition of stem-like features is achieved primarily by epigenetic mechanisms, our goal was to identify long noncoding RNAs (lncRNAs) involved in promoting the CSC phenotype in PDAC. For this purpose, we analyzed the lncRNA expression profile of established CSC-enriched tumorsphere cultures of PDAC patient-derived xenograft (PDX) tumors.

Methods



Results

We identified 19 upregulated lncRNAs and 6 downregulated lncRNAs in CSC-enriched tumorsphere cultures of PDAC patient-derived xenograft (PDX) tumors.

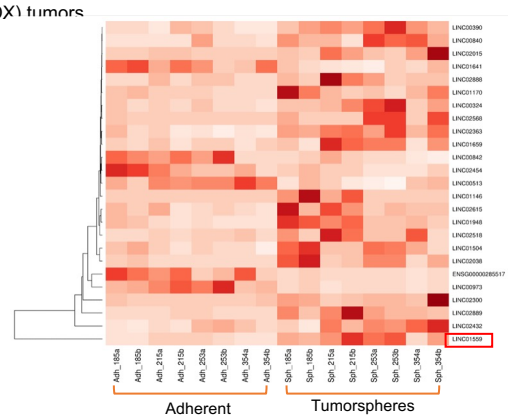


Figure 1: **Heatmap the CSC-enriched lncRNA transcriptional profile.** LncRNA transcriptional profile of 4 PDAC patient-derived xenograft (PDX) tumors comparing primary tumorsphere cultures (CSC enriched) with primary adherent cultures (non-CSC enriched). LINC01559 is highlighted.

Of the upregulated lncRNAs, LINC01559 was the most promising. Its expression was increased in PDAC cell line (AsPC-1) tumorspheres and experiments published by our group showed that this lncRNA promotes PDAC cell migration and invasion (Paixão et al, 2022).

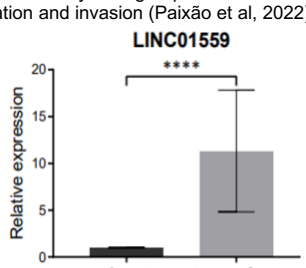


Figure 2: **LINC01559 expression is increased in AsPC1 tumorspheres by qRT-PCR.** Statistical significance was measured using the t test, $p < 0.05$.

To determine whether LINC01559 is associated with PDAC prognosis, we correlated its expression level with PDAC patient survival using publicly available TCGA (the Cancer Genome Atlas) RNAseq and clinical datasets.

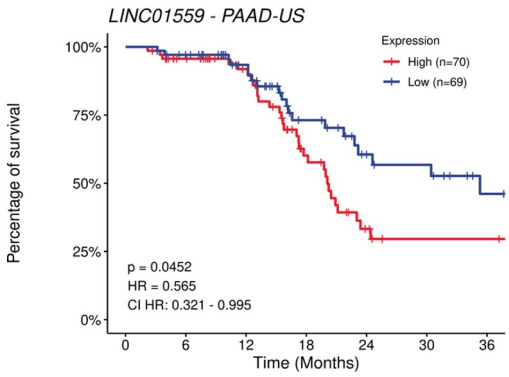


Figure 3: High expression of LINC01559 is significantly associated with shorter PDAC patient survival. Patients were grouped into two LINC01559 expression groups (high and low), according to the median expression in all samples. Kaplan-Meyer survival curves were generated using the R survival package. Survival curves were compared by the log-rank test with a significance threshold of $p < 0.05$.

In parallel, in order to correlate LINC01559 expression with the transformed phenotype in PDAC, we analyzed single-cell RNAseq datasets of PDAC tumors. LINC01559 is enriched in type 2 ductal cells, which are found exclusively in PDAC tumors and represent the malignant cell population (4).

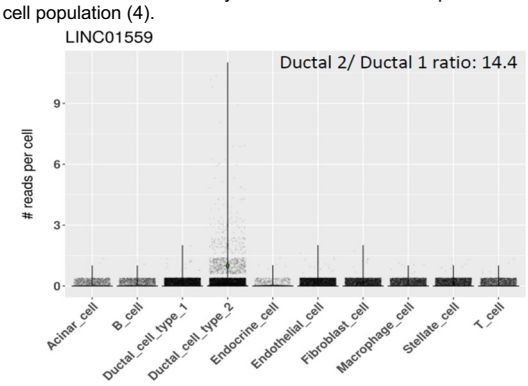


Figure 4: LINC01559 is enriched in malignant type 2 PDAC cells. Violin chart demonstrating normalized read counts (y-axis) of LINC01559 in 10 PDAC cell types (x-axis) reported in single cell RNA-seq analysis of 57,530 cells from 24 PDAC and 11 non-tumor pancreatic samples (Peng et al., 2019). Chi-square test, $p < 0.00001$.

Conclusion

We have identified lncRNAs differentially expressed in PDAC CSCs and our results indicate that LINC01559 may represent a promising PDAC biomarker or therapeutic target, as it is associated with PDAC aggressiveness and a worse clinical prognosis.

Reference

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