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MicroRNAs: Biomarkers and therapeutic targets in drug resistant pancreatic cancer

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Background: Pancreatic cancer is highly fatal due to both intrinsic (de novo) and extrinsic (acquired) resistance to conventional therapeutics. The drug resistance phenotype is in part due to the acquisition of Epithelial-to-Mesenchymal Transition (EMT) which is reminiscent of the acquisition of cancer stem cell (CSC)/Cancer Stem like Cells (CSLC) characteristics, and all of which are associated with resistance to conventional therapeutics. Emerging evidence suggests that CSCs/CSLCs have the capacity for increased cell growth, cell migration/invasion, metastasis, and treatment resistance, which leads to poor clinical outcome. However, the molecular role of CSCs/CSLCs in tumor development and progression is poorly understood. Since there is no curative treatment for patients diagnosed with pancreatic ductal adenocarcinoma (PDAC), innovative treatment options are urgently needed to overcome resistance in order to improve therapeutic outcome of PDAC. Therefore, mechanistic understanding and targeted killing of CSCs/CSLCs may provide a newer therapeutic strategy for the treatment of PDAC. It has been well accepted that microRNAs (miRNAs) play critical roles during tumor development and progression through deregulation of multiple genes. Moreover, deregulated expression of miRNAs may also play a key role in the regulation of CSC/CSLC characteristics and functions.

Aim: The aim of this study was to investigate the role of miRNA in designing novel therapies for PDAC by targeting CSCs/CSLCs.

Methods: Multiple molecular biological methods were implemented and cell sorting was done to obtain CSLCs for cultured PC cells. These cells were interrogated for molecular studies and further extended to assess the activity of a miRNA targeted agent (CDF: a novel agent discovered by our laboratory) for the development of future treatment of PC.

Results: We found that isolated CD44(+)/CD133(+)/EpCAM(+) cells (triple-marker-positive cells) from human PC cell lines, MiaPaCa-2 and L3.6pl cells, display aggressive characteristics, such as increased cell growth, clonogenicity, cell migration, and self-renewal capacity, which is consistent with overexpression of CSLC signatures/markers. We also found deregulated expression of over 400 miRNAs, including let-7, miR-30, miR-125b and miR-335 in CSLCs. As a proof-of-concept, knockdown of miR-125b resulted in the inhibition of tumor cell aggressiveness of CSLCs (triple-marker-positive cells), consistent with the down regulation of CD44, EpCAM, EZH2 and snail. We also found that CDF was an effective agent in the re-expression of miRNAs that were typically lost in CSLCs.

Conclusions: In conclusion, the current results clearly suggest the importance of miRNAs in the regulation of CSLC characteristics and may serve as novel targets for therapy. Moreover, the miRNA targeting activity of CDF would likely lead to the clinical development of CDF for eradicating CSLCs for the treatment of PDAC with better therapeutic outcome.

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