GONIOTHALAMIN N-ACETYLATED-AZA-DERIVATIVE AS A NOVEL MIRNA-REGULATING SMALL MOLECULE THAT EFFECTIVELY SUPRESSES KEY MARKERS OF PANCREATIC CANCER AGGRESSIVENESS.

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Pancreatic cancer is characterized by genetic alterations that induce tumorigenesis and determine the aggressive phenotype of the disease. It ranks fourth among cancer related deaths in United States. Pancreatic cancer aggressiveness is closely related to high levels of pro-survival mediators, which lead to rapid disease progression, metastasis and resistance. microRNAs (miRNAs) have a variety of roles in the development and progression of cancer. The clinical potential of miRNAs based on the fact that a single miRNA can regulate multiple oncogenic pathways commonly deregulated in cancer. Recent studies have been undertaken to identify miRNA-regulating small molecules. Our group have demonstrated that a goniothalamin N-acylated aza-derivative (derivative 8) downregulates mediators of signaling transduction associated with pancreatic cancer aggressiveness. Now, we investigated if this compound is effective in modulating miRNAs that target proteins involved with pancreatic cancer aggressiveness. Our data demonstrate the ability of the derivative 8 in up- and down-regulation miRNAs in human pancreatic cancer cells (Panc-1). The global analysis of microRNA expression revealed that the derivative 8 modulated 12 miRNAs in Panc-1 cells, among them 10 miRNAs were up-regulated (miR-3960, miR-155, miR-193a-3p, miR-299, miR-1224, miR-550, miR-3909, miR-34b, miR-3921, miR-4701-3p) and 2 miRNAs were down-regulated (miR-3687, miR-4417). Interestingly, the increase of miR-155, miR-1224, miR-299 and miR-34b are associated with the reduction of Ciclin-D1, VEGF, BAX, AXL, c-MYC, BCL-2, CDK6 and SMAD3 protein levels. Thus, we suggest that the action of derivative 8 in pancreatic cancer cells involves the reduction the aggressiveness mediators, as consequence of up-regulation of miRNAs. In conclusion, our findings indicate that derivative 8 can be classified as miRNA-regulating small molecule and also highlight that the microRNA profiling can be a step in the pipeline for drug discovery.

Keywords: miRNA-regulating small molecules, pancreatic cancer; aggressiveness.

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