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Role of miR-29 in pancreatic cancer and its potential use as a therapeutic agent

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Pancreatic Ductal Adenocarcinoma (PDAC) is one of the leading causes of cancer deaths in western society, with the worst prognosis. In spite of intense research efforts and the development of numerous new cancer drugs and treatment strategies over the past four decades, there have been no significant improvements in overall patient survival, and death rates are almost equivalent to incidence rates. Dense fibrotic stroma associated with PDAC tumor plays a critical role in PDAC progression/metastasis and drug delivery to the tumor bed. Targeting stroma is considered as a potential therapeutic strategy to improve anti-cancer drug efficacy and patient survival. Although numerous stromal depletion therapies have reached the clinic, they add little to overall survival and are often associated with toxicity. Furthermore, increasing evidence suggests the anti-tumor properties of stroma. Its complete ablation enhanced tumor progression and reduced survival. These conflicting reports indicate the need to understand the molecular mechanisms associated with PDAC tumor-stromal interactions in order to develop new and effective treatments for PDAC. miRNAs are conserved, non-coding RNAs that regulate eukaryotic gene expression and are critical to the maintenance of cellular homeostasis. A single miRNA regulates hundreds of genes, often targeting multiple components of complex, inter- and intracellular networks. Thus, misregulation of a single miRNA can have a profound impact on cellular physiology that leads to disease(s). A large body of evidence demonstrates the role of miRNAs in cancer pathogenesis in wide variety of tumor types, including PDAC and their potential use as anti-cancer agents. In an effort to understand the role of miRNAs in disease mechanisms associated with PDAC tumor-stromal interactions, using *in vitro*, *in vivo*, and patient biopsies, we found loss of miR-29 in pancreatic stellate cells, the critical stromal cells responsible for fibrotic stroma, and cancer cells. Restored expression of miR-29 in stromal cells reduced accumulation of major stromal matrix proteins and cancer growth in culture. Furthermore, overexpression of miR-29 in cancer cells reduced cancer cell migration/anchorage independent growth and sensitized them to gemcitabine by inhibiting autophagy. Based on these observations, my laboratory is further expanding to dissect the mechanistic role of miR-29 in PDAC and develop miR-29 based therapeutic strategy.

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