Medical Sciences

miR-145: Revival of a Dragon in Pancreatic Cancer

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Emergence of the role of MicroRNA-145 (miR-145) as a tumor suppressor in pancreatic cancer, offers its potential for novel therapeutic interventions. Our recently published studies demonstrate clinical significance of miR-145 in pancreatic cancer and suggest that the dysregulation of miR-145 in human pancreatic tumors draws in parallel with the aberrant expression of an oncogenic mucin, MUC13. These studies also present a novel therapeutic strategy of restoring the downregulated levels of miR-145 in pancreatic cancer via nanoparticle mediated efficient delivery system.

microRNA-145 | Tumor suppressor | Pancreatic cancer | MUC13 | Nanoparticles

Highest mortality rate of pancreatic cancer is mainly attributed to the lack of early diagnosis and effective treatment modality. Emphasizing on new therapeutic interventions, microRNAs may act as strong players in this devastating scenario. MicroRNAs (miRNAs) are endogenously expressed, small (18–25 nucleotides) non-coding RNAs, which directly bind to the 3′-untranslated regions of the target messenger RNAs and regulate the expression of many genes. Various miRNAs-based therapeutic strategies are investigated in cancer for their efficient delivery (tumor suppressor miRNAs) or inhibition (oncogenic miRNAs) in cancers. Some miRNAs have also entered preclinical and clinical trials for use in humans. MicroRNA-145 (miR-145) is downregulated in several cancers such as hepatocellular [3], head and neck [1], thyroid [2], breast [4], colon [5] and lung cancers [6] which contributes to enhanced oncogenic cellular processes such as, cell cycle, proliferation, differentiation, invasion, migration [7, 8]. Our study, published in Oncotarget, first time reported miR-145 as tumor suppressor in pancreatic cancer [9]. The article summarizes a novel miR-145-regulated mechanism controlling aberrant MUC13 expression in pancreatic cancer. This study provides a preclinical proof of concept suggesting that miR-145 restitution might improve therapeutic outcomes in pancreatic cancer by directly targeting and post-transcriptionally modifying/inhibiting mucin MUC13 which is aberrantly expressed in pancreatic cancer [10]. Our results show that the inhibition of MUC13 expression on miR-145 restitution accompanies the alteration of its related target proteins, thereby reducing tumor growth and invasiveness in pancreatic cancer cells and xenograft mice. The outcomes of these preclinical studies in xenograft mice hence affirmed the ability of miR-145 restitution to inhibit MUC13 associated molecular changes ultimately leading to reduction in tumor growth. These changes involve the reduction in the expression of downstream targets of MUC13 such as, HER2, PAK1, AKT and enhanced expression of p53. Altogether, the restoration of miR-145 significantly inhibits pancreatic cancer cell proliferation, invasion, migration and promotes gemcitabine sensitivity. Furthermore, the results in this article demonstrate an interesting inverse correlation of MUC13 with miR-145 expression in human pancreatic cancer tissues (Pancreatic Intraepithelial Neoplasia lesions and pancreatic ductal adenocarcinoma) that further provides a clinical validation of the identified outcomes.

Despite the exciting and promising therapeutic potential of tumor suppressor miRNAs, including miR-145, the successful delivery remains a challenge for their transition to clinical applications for human use. Nanoparticles are faced to overcome physical as well as biological barriers, such as diffusion, aggregation, adsorption, phagocytic sequestration, stability and renal clearance. Considering this fact, we have therefore, generated a magnetic nanocarrier system for the successful intracellular delivery and sustained release of miR-145 to pancreatic cancer cells. The design and outcomes of this study are discussed in "Journal of Gastrointestinal Surgery" [11]. The magnetic nanoformulation is fabricated with several coatings that include β-cyclodextrin, pluronic polymer (F-127) and branched Polyethylenimines (PEI), which significantly increases miR-145 encapsulation and minimizes aggregation or toxicity in systemic circulation. This magnetic nanoformulation efficiently escapes endosomal and lysosomal degradation and delivers miR-145 to pancreatic cancer cells through enhanced permeation and retention (EPR) effect [11, 12]. Delivery of miR-145 using this formulation goes together with restoring miR-145 levels in cells and inhibiting MUC13 and its downstream effectors; the molecular changes leading to reticence of metastatic characteristics such as invasion, migration and motility of pancreatic cancer cells.

In conclusion, our published articles have a number of significant things to say that ranges from the clinical significance of miR-145 in pancreatic cancer to its therapeutic implications and describe the development of its efficient delivery system (Figure 1). miR-145, being a universal tumor suppressor in cancers wherein identified, eases out the apprehensions with regard to its effects on other organs; actually hitting the malignant cells, thus, prospecting it as a potent therapeutic modality for pancreatic cancer treatment, either alone or combination with chemotherapeutic drugs. The end-outcome measurements are strongly related to smart voyage of the nanoparticle system that leads to the transportation and function of the miR-145, in its mature form. Additionally, in order to specifically target the desired tumor for enhanced accumulation of miR-145, the formulation can be modified for active targeting by conjugating with pancreatic tumor specific antibodies/aptamers, such as MUC13. These strategies will be beneficial for designing targeted therapies with enhanced accrual of miR-145 at the tumor site.

Conflict of Interest: No conflicts declared.

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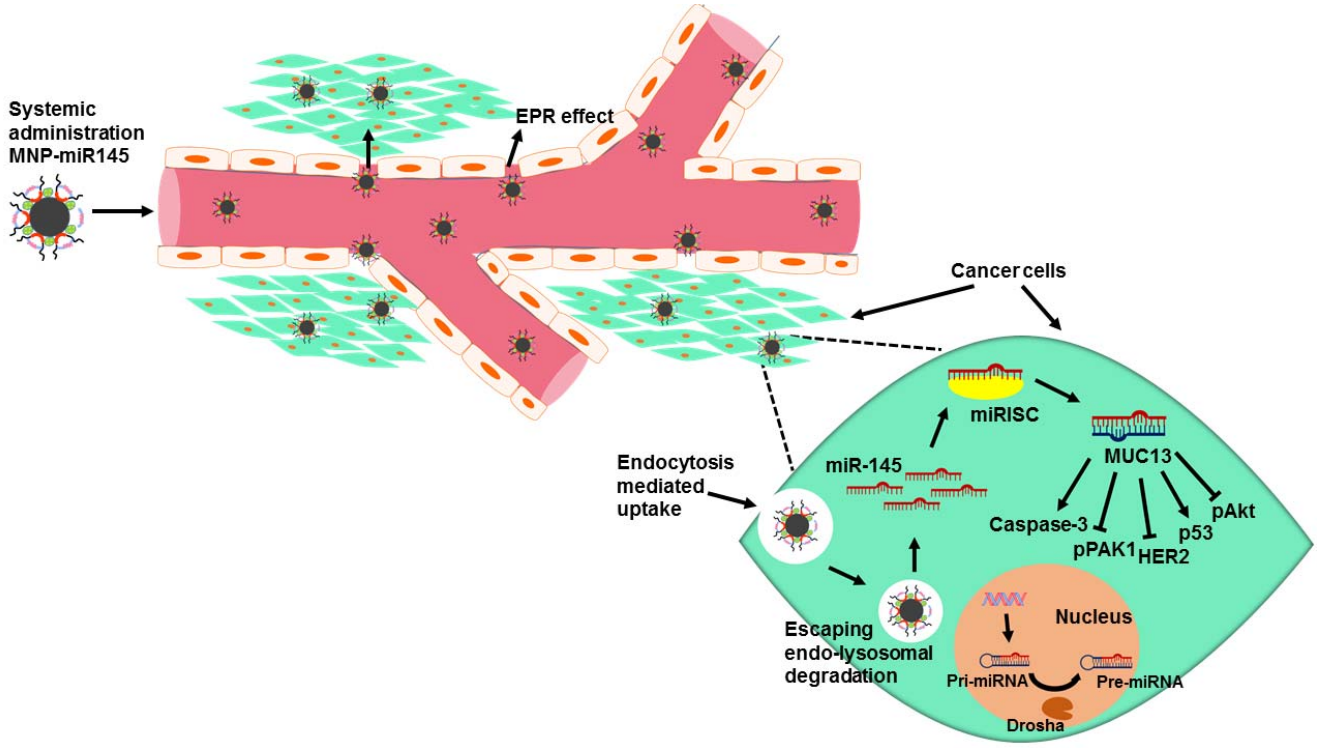

Figure 1. Schematic representation illustrating the delivery of miR-145 and its molecular effects in pancreatic ductal adenocarcinoma.

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