MicroRNAs as potential therapeutic targets for pancreatic cancer

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Abstract

Pancreatic cancer is one of the most aggressive malignancies. The poor prognosis of pancreatic cancer patients is mainly attributed to low diagnostic rate at the early stage, highly aggressive nature coupled with the inadequate efficacy of current chemotherapeutic regimens. Novel therapeutic strategies are urgently needed for pancreatic cancer. MicroRNAs (miRNAs) play an important regulatory role in key processes of cancer development. The aberrant expression of miRNAs is often involved in the initiation, progression, and metastasis of pancreatic cancer. The discovery of tumor suppressor miRNAs provides prospects for the development of a novel treatment strategy for pancreatic cancer. We reviewed recent progress on the understanding of the role of miRNAs in pancreatic cancer, highlighted the efficient application of miRNAs-based therapies for pancreatic cancer in animal models and clinical trials, and proposed future prospects. This review focuses on the promise of integrating miRNAs into the treatment of pancreatic cancer and provides guidance for the development of precision medicine for pancreatic cancer.

Keywords: Pancreatic cancer; MicroRNA; MicroRNA carriers; Precision medicine

Introduction

Pancreatic cancer is one of the most devastating digestive malignancies with the worst prognosis, and the incidence is on the rise annually.[1] The poor prognosis of pancreatic cancer patients is mainly attributed to low surgical resection rates, poor sensitivity to chemoradiotherapy, and high recurrence and metastasis rates. Radical surgical resection plus perioperative chemotherapy is the standard treatment for pancreatic cancer, but the efficacy is unsatisfactory. Intravenous chemotherapeutic agents are difficult to reach effective therapeutic concentration within the tumor for maximum bioactivity due to the nature of poor blood supply and dense fibrous stroma and immunosuppressive microenvironment in pancreatic cancer tissue. Improved understanding of the core mechanism related to the initiation and progression of pancreatic cancer will help to develop effective therapeutic agents.

MicroRNAs (miRNAs) are a class of 19 to 23 nucleotides base of non-coding single-stranded endogenous RNAs first discovered by Lee *et al*[2] in 1993. MiRNAs regulate gene expression at post-transcriptional levels by binding to the 3′ untranslational region of the target messenger RNAs (mRNAs) and inducing mRNAs degradation or translation repression. About 60% of the coding genes are regulated by miRNAs. miRNAs have been reported to be involved in the occurrence, progression, and metastasis of a variety of cancers. Consequently, miRNAs could not only function as candidate diagnostic markers of malignancies but also be identified as potential therapeutic targets of cancers.

Therefore, here, we aim to provide a systematic review on the current status of the understanding of the role of miRNAs in pancreatic cancer and the potential application of miRNAs in pancreatic cancer therapy. In particular, we explore the molecule mechanisms by which miRNAs participate in pancreatic cancer development and how to target miRNAs in pancreatic cancer treatment.

Targeting miRNAs in Pancreatic Cancer Treatment

MiRNAs play an important role in the development and progression of pancreatic cancer. MiRNAs could be divided into two categories: oncogenic miRNAs and tumor suppressor miRNAs, according to the role of target mRNA in tumor progression. The function of oncogenes and tumor suppressor genes comes to an optimal balance under normal conditions. The oncogenic miRNAs inhibit the expression of tumor suppressor genes, while tumor suppressor miRNAs inhibit the expression of oncogenes. The dysregulation of tumor suppressor or oncogenic miRNAs will break the dynamic balance between oncogenes and tumor suppressor genes, and finally

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promote the occurrence and development of tumors. The introduction of oncogenic miRNA antagonist and tumor suppressor miRNAs can exert anti-cancer effect by inhibiting pancreatic cancer cell proliferation and invasion, promoting apoptosis, and enhancing chemosensitivity, providing the basis for the application of miRNAs in the treatment of pancreatic cancer.

Tumor suppressor miRNAs

Overexpression of tumor suppressor miRNAs could exert anti-tumor effects by inhibiting the progression of pancreatic cancer (summarized in Table 1). Zhan *et al*[17] found that the overexpression of miR-455-3p suppressed pancreatic cancer progression via inhibiting transcriptional co-activator with PDZ-binding motif (*TAZ*)-mediated Wnt/catenin signaling pathway, and promoted the apoptosis of pancreatic cancer cells by regulating the expression of apoptosis-related proteins Bcl-2, and Bax. Hu *et al*[18] reported that miR-373-3p could downregulate the expression of *Cycin D2*, enhance the chemosensitivity to gemcitabine, and inhibit the growth of gemcitabine-resistant pancreatic cancer cells.

Single miRNA could target different mRNAs, and the same mRNA could be regulated by different miRNAs. miR-145 was found to regulate different targets to inhibit the progression of pancreatic cancer. miRNA-145 was reported to suppress the expression of TGF-β receptor and *SMAD2*, *mucin 13*, and neural precursor cell expressed, developmentally down–regulated 9 (*NEDD9*) to inhibit the proliferation, migration, and invasion of pancreatic cancer cells and enhance the chemosensitivity to gemcitabine.[19-21] Wang *et al*[22] found that miRNA-145 could inhibit cancer cell invasion, growth, and angiogenesis by downregulating angiopoietin-2 (Ang-2). Patel *et al*[23] found that let-7 could inhibit the progression of pancreatic cancer cells by enhancing the expression of suppressor of cytokine signaling 3 (*SOCS3*) to inhibit the phosphorylation of STAT3. Liu *et al*[24] found that miR-708 inhibited the proliferation and chemoresistance of pancreatic cancer cells by suppressing the expression of survivin. Ma *et al*[25] reported that lncRNA H19 could promote pancreatic ductal adenocarcinoma cell invasion and migration by antagonizing let-7 to increase the expression of high mobility group A2 (HMGA2). miR-34 could act as a tumor suppressor in pancreatic cancer via regulating multiple signaling pathways. miR-34a inhibited the expression of *Snail1* and *Notch 1* via post-transcriptional regulation, inducing apoptosis and suppressing the migration and invasion of cancer cells. The downregulation of *Notch 1* increased the expression of miR-34a, forming a positive feedback loop between miR-34a and *Notch 1*.[26] miR-34 could also enhance the sensitivity of pancreatic cancer cells to gemcitabine and promote apoptosis by downregulating the expression of *Slug*.[27] An *et al*[28] also reported that miR-203a-3p could inhibit the proliferation and epithelial–mesenchymal transition (EMT) of pancreatic cancer cells by downregulating *Slug*.

Oncogenic miRNAs

Oncogenic miRNAs promote the progression of pancreatic cancer by regulating different targets (summarized in Table 2). The introduction of miRNA antagonists can inhibit carcinogenic miRNA and exert an anti-cancer effect. miRNA antagonists are single-stranded antisense oligodeoxynucleotides (ASO) targeting carcinogenic miRNAs, which could provide high stability, high affinity, and antinuclease protection for miRNAs through chemical synthesis and specific modification. Li *et al*[43] found that exosome miR-5703 derived from pancreatic cancer stellate cells could directly downregulate target gene CKLF (chemokine-like factor)-like MARVEL transmembrane domain containing family member 4, and promote the proliferation of pancreatic cancer cells by activating PI3K/Akt signaling

Table 1: Summary of tumor suppressor miRNAs in pancreatic cancer.

miRNA	Function	Target gene	Author	Publication year
miR-429	Increase chemosensitivity to gemcitabine	PDCD4	Yu *et al*[3]	2017
miR-205	Inhibit proliferation, invasion, migration, and increase chemosensitivity to gemcitabine	Not mentioned	Chaudhary *et al*[4]	2017
miR-217	Inhibit proliferation, invasion, and promote apoptosis	E2F3	Yang *et al*[5]	2017
	Inhibit invasion and migration	ANLN	Idichi *et al*[6]	2017
	Inhibit proliferation, invasion, and migration	Tpd52l2	Chen *et al*[7]	2017
miR-221	Induce autophagy and apoptosis	HDAC6	Yang *et al*[8]	2018
	Inhibit proliferation	SOCS3	Xie *et al*[9]	2018
miR-876-3p	Inhibit proliferation, invasion, migration, and promote apoptosis	JAG2	Yang *et al*[10]	2018
miR-675	Inhibit proliferation	E2F-1	Ma *et al*[11]	2018
miR-98-5p	Inhibit proliferation, invasion, and metastasis	MAP4K4	Fu *et al*[12]	2018
miRNA-339-5p	Inhibit invasion and migration	ZNF689	Yu *et al*[13]	2019
miR-142-5p	Inhibit proliferation and promote apoptosis	RAP1A	Yao *et al*[14]	2019
miRNA-33b	Inhibit proliferation, invasion, andmigration	MMP16	Luo et al[15]	2020
miR-4516	Inhibit proliferation, invasion, migration, and promote apoptosis	OTX1	Chen *et al*[16]	2020

miRNAs: MicroRNAs; SOCS3: suppressor of cytokine signaling 3.

Table 2: Summary of oncogenic miRNAs in pancreatic cancer.

miRNA	Function	Target gene	Author	Publication year
miR-196a	Promote proliferation, invasion, and migration, and inhibit apoptosis	ING5	Liu *et al*[29]	2013
miR-221	Promote proliferation	PTEN, p27kip1, p57kip2, and PUMA	Sarkar *et al*[30] Yang *et al*[31]	2013 2016
miR-371-5p	Promote proliferation	ING1	He *et al*[32]	2014
miR-301b	Promote invasion, migration, and resistance to gemcitabine	TP63	Funamizu *et al*[33]	2014
miR-221-3p	Promote proliferation, invasion, migration, and resistance to 5-FU	RB1	Zhao *et al*[34]	2016
miR-451	Promote proliferation and migration	CAB39	Guo *et al*[35]	2017
miR-301a-3p	Increase chemoresistance to gemcitabine	PTEN	Xia *et al*[36]	2017
miR-106b	Increase chemoresistance to gemcitabine	TP53INP1	Fang *et al*[37]	2019
miR-302a-3p	Promote invasion and migration	SOCS5	Zhang *et al*[38]	2019
miR-132	Promote proliferation and inhibit apoptosis	Shh	Zhao *et al*[39]	2019
miR-132	Promote proliferation, invasion, and migration	PTEN	Zhang et *al*[40]	2019
miR-210	Increase chemoresistance to gemcitabine	Not mentioned	Yang *et al*[41]	2020
miR-193a-5p	Promote invasion and migration	SRSF6	Li *et al*[42]	2020

miRNAs: MicroRNAs; 5-FU: 5-fluorouracil.

pathway through p21-activated kinase 4. miR-21 could exert an oncogenic role in pancreatic cancer by regulating multiple cancer-associated signaling pathways. Cancer-associated fibroblasts with high miR-21 expression could promote the migration of pancreatic cancer cells and enhance gemcitabine resistance via elevating the expression of matrix metalloproteinase 3, matrix metalloproteinase 9 (MMP-9), and platelet-derived growth factor.[44] Overexpression of miR-21 could increase drug resistance to 5-fluorouracil and promote the proliferation of pancreatic cancer cells via downregulating the expression of target genes *PTEN* and *PDCD4*.[45] Zhao *et al*[46] reported a positive feedback loop between miR-21 and *epidermal growth factor (EGF)* signaling cascade in pancreatic cancer. *EGF* promoted the expression of miR-21, while miR-21 could enhance the activity of *EGF* by inhibiting *EGF* inhibitors. In addition, miR-21 could activate MAPK/ERK and PI3K/AKT signaling pathways to promote *EGF*-induced proliferation and suppress the apoptosis via inhibiting targeted gene Sprouty2, which constitutes the self-reinforcing circuit of this pathway. Sun *et al*[47] proposed that the downregulation of miR-21 could increase the expression of Von Hippel-Lindau tumor suppressor in pancreatic cancer. miR-21 could suppress the proliferation of pancreatic cancer cells via inhibiting the HIF-1α/VEGF signaling pathway and suppressing the expression of matrix metalloproteinase 2 and MMP-9. miR-155 is a key molecule to promote the progression of pancreatic cancer. miR-155 could target *Foxo3a* to promote the proliferation of pancreatic cancer cells induced by Reactive Oxygen Species generation.[48] miR-155 could also downregulate the expression of suppressor of cytokine signaling 1 and *SOCS3* to increase the activation of STAT3 and promote the proliferation and invasion of pancreatic cancer cells.[49,50]

Different studies demonstrated the opposite role of miR-203 in pancreatic cancer, which implies the differential and individualized gene expression among pancreatic cancers. miR-203 was reported to promote the proliferation, migration, and invasion of pancreatic cancer cells by inhibiting the expression of salt-inducible kinase 1 and *SOCS3*.[51,52] On the other hand, miR-203 was reported to inhibit pancreatic cancer cell proliferation and induce apoptosis and G1 phase cell cycle arrest by targeting *Survivin*.[53] Du *et al*[54] reported that miR-203 could inhibit the expression of *DJ-1* and increase the expression of *PTEN* to inhibit the proliferation, induce apoptosis, and reduce cisplatin resistance of pancreatic cancer cells. Miao *et al*[55] also found that miR-203 inhibited tumor cell migration and invasion by upregulating the expression of *caveolin-1* in pancreatic cancer cells.

Tumor suppressor miRNAs could degrade targeted mRNAs to inhibit the progression of pancreatic cancer, and miRNA antagonists could reduce tumor dissemination by blocking the function of oncogenic miRNAs, providing the basis of integrating miRNAs into the treatment of pancreatic cancer.[56-65] However, the introduction of a single miRNA mainly targets one target, and the effect might be generally temporary. In addition, miRNAs have some disadvantages such as high hydrophilicity, poor membrane penetration, and the susceptibility to be cleared by the kidney, which limit their clinical application.

MiRNA Vectors for Pancreatic Cancer Therapy

MiRNA could induce post-transcriptional downregulation by binding to target mRNA in a sequence-specific way, but it is difficult to enter the cells due to the negative charge repulsion of the cell membrane. Therefore, it is urgent to choose and design effective carrier to deliver miRNA through the dense fibrous stroma to achieve effective concentration in the tumor tissue, and enhance intracellular uptake to maximize the bioactivity.

Viral vector

The virus could be used to deliver miRNA as a carrier after detoxifying treatment. Hu *et al*[66] reported that intra-

tumoral injection of an adenovirus vector to deliver miR-143 could significantly inhibit tumor progression in a xenograft tumor model. The liver metastatic lesions of mice were significantly suppressed after inoculating ad-miR-143 infected cells in the liver metastasis model. Sicard *et al*[56] constructed lentivirus vector (LV) (a/miR-21) by using LVs to deliver anti-miRNA, and they confirmed that the proliferation of pancreatic cancer cells was inhibited in a dose-dependent manner in mice. Chaudhary *et al*[4] reported that the overexpression of miR-205 mediated by LVs could enhance the chemosensitivity of pancreatic cancer stem cells and inhibit the proliferation of tumor cells. HIV-1-based LVs were more effective than other vectors such as adenovirus and SV40 and did not affect the production of endogenous miRNA. However, LVs-based vectors might lead to genotoxicity, unpredictable risk of insertion mutations, activation of proto-oncogenes, and even aberrant transcripts.

Nanoparticles and liposome carriers

Although the miRNA delivery system based on viral vectors is efficient, the toxicity and immunogenicity of viruses limit their further applications compared with non-viral vectors such as nanoparticles and exosomes. Nanoparticle packaged oligonucleotides are considered to be safer and more efficient. Gilles *et al*[57] designed targeted nanoparticulate carriers coated with oligonucleotide analogs iRGD-TPN-21, which could selectively deliver anti-miR-21 to the tumor site and inhibit tumor progression in a dose- and time-dependent manner. Passadouro *et al*[58] constructed a novel liposome nano-system by coating cationic liposomes with albumin, which could effectively transfer ASO to pancreatic cancer cells and suppress the expression of miR-21, miR-10b, miR-221, and miR-222. Ferino *et al*[59] designed a novel vector based on palmityl-oleoyl-phosphatidylcholine liposomes conjugated with lipid-modified cell- penetrating peptide and coated with single-stranded miR-216b mimic. The target KRAS protein was reduced by about 70% and colony formation was inhibited by about 40% *in vitro*. miRNAs packaged by nano-systems could precisely target pancreatic cancer, avoid the risk of genotoxicity and insertion mutation caused by LVs, and increase significantly the efficiency of chemotherapeutic drugs. The nano-systems provide promising prospects for clinical application.

Exosome carrier

The exosome is composed of unique lipids and proteins as a kind of endogenous nanoparticles, with several advantages such as natural stability, better immunocompatibility, specific targeting ability, and abundant drug loading. Many proteins on the surface of the exosome could be modified and exosomes could be used as new drug delivery carriers. The hucMSC-derived exosome vector constructed by Ding *et al*[60] could transfer miR-145-5p through endocytosis. Intratumoral injection of exo-miR-145-5p into nude mice bearing human pancreatic cancer cells could significantly inhibit the proliferation and invasion of pancreatic cancer cells and promote apoptosis and cell cycle arrest. Zuo *et al*[61] isolated exosomes from HEK293 cells and synthesized exosomes coated with miR-34a by ultrasound, which could significantly inhibit the progression of pancreatic cancer *in vivo* and *in vitro*. The unmodified exosomes could be easily cleared by the liver intravenously and showed minimal tumor accumulation.[67]

Application of miRNA-Based Drugs in Pancreatic Cancer

Many mechanisms are involved in the development of pancreatic cancer. Therefore, the combination of two or more drugs with different mechanisms, such as targeted drugs based on different miRNAs or the combination of miRNA-based drugs and chemotherapeutic agents, might significantly inhibit tumor progression through synergistic effects. Passadouro *et al*[58] treated pancreatic cancer cells with anti-miRNA oligonucleotides or chemotherapeutic drug sunitinib, and the cell survival rate decreased by about 21% compared with the control group, while the combination of oligonucleotide anti-miR-21 and sunitinib resulted in a decrease of 45% in cell viability. Uz *et al*[62] developed a dual drug delivery nano-device to deliver miR-345 and gemcitabine, which could stably release miR-345 and gemcitabine to effectively suppress tumor progression and metastasis. Li *et al*[63] developed a novel nanoparticle for targeted co-delivery of miRNA-21 (ASO-miR-21) and gemcitabine, and it could achieve active and targeted delivery and protect ASO from enzymatic degradation. The nanoparticle could significantly inhibit the EMT of pancreatic cancer cells and reduce liver metastasis.

Based on the overexpression of epidermal growth factor receptor (EGFR) in nearly 95% of pancreatic cancer patients, Mondal *et al*[64] prepared mixed micelle for the co-delivery of gemcitabine and miR-205, and it was decorated with EGFR-targeting cetuximab (C225) monoclonal antibody to achieve targeted delivery. The micelle significantly reversed gemcitabine resistance and inhibited the progression of advanced pancreatic cancer. Kumar and colleagues synthesized self-assembled micromicelles targeting tumor suppressor miR-let7b with Hedgehog pathway inhibitor GDC-0449.[68] Nearly 80% of GDC-0449 was continuously released from the polymer within 2 days, and miRNA could be stable for 24 h in the presence of serum.

The combination of multiple drugs could achieve a synergistic anti-tumor effect at a lower dose. In most studies, the two drugs were given separately by different drug delivery systems.[58,69] However, there are some disadvantages to using two different carriers, including different biocompatibility and biological distribution, increased drug toxicity, and decreased bioactivity of the drug combinations. The design of a single nano-device as an effective co-delivery carrier could promote drug targeting and internalization, achieve stable and continuous co-release of drugs, improve the therapeutic effect and reduce side effects. Although these targeted miRNA therapeutic delivery systems enhanced bioactivity in tissue culture and mouse models, it is unclear whether they can achieve the same effects in humans.

Clinical Trials of miRNAs for Pancreatic Cancer Therapy

Nucleic acid therapeutics based on RNA therapy could induce target-specific inhibition. Compared with tradi-

tional targeted therapy, the regulation of mRNA might exert faster and more lasting effects. Tumor suppressor miRNA is introduced to restore its expression in cancer to induce the sequence-specific degradation of target mRNA and has a promising application prospect. Beg *et al*[70] reported the first phase I clinical trial of miRNA-based cancer therapy (MRX34) (serial number: NCT01829971). MRX34 is a liposomal formulation based on tumor suppressor miR-34a. A total of 47 adult patients with refractory advanced solid tumors were included in this clinical trial, including five cases of pancreatic cancer. They received MRX34 therapy twice a week for 3 weeks, with a cycle of 4 weeks. The most common adverse reactions included fever, fatigue, and back pain. Therefore, miRNA-based therapeutics with MRX34 were effective, tolerable, and feasible. However, Hong *et al*[71] reported that four patients died due to severe immune-mediated adverse reactions in the follow-up study and the trial ended prematurely. In this trial, among 66 patients who could be assessed,16 patients achieved clinically significant stable disease for ≥ 4 cycles and three patients reached partial responses (PRs). Golan *et al*[72] reported an open-label phase 1/2a clinical trial (serial number: NCT01188785) in inoperable locally advanced pancreatic cancer. In this trial, miniature biodegradable implant siG12D-LODER^{TM} which could release siRNA drug against KRAS(G12D) was inserted into pancreatic tumors combined with gemcitabine chemotherapy. Among 12 patients who were evaluated, ten patients were in stable condition and two patients reached PR. The most common adverse reactions were grade one or two (89%), such as transient abdominal pain, diarrhea, and nausea. Intratumoral injection of siRNA combined with chemotherapy was confirmed to be well tolerated with good safety and potential efficacy. Therefore, in future studies, we should design an effective miRNA carrier to avoid systemic immune activation and predict the toxic side effects of these drugs, especially the immune-associated adverse effects in the subsequent clinical trials.

Conclusion and Future Prospect

MiRNAs play an important regulatory role in the progression of pancreatic cancer. The latest advances in the delivery vector and therapeutic application of miRNAs in pancreatic cancer provide new ideas and directions for pancreatic cancer treatment [Figure 1]. The function and expression level of miRNAs differ not only in normal and diseased tissues and organs but also in different stages of the disease and different patients.[9,23,27,28,51-55] The identification of cancer-specific and core miRNAs of pancreatic cancer is the key to achieve the clinical application of miRNAs-based therapy. The first clinical trial of miRNA-based therapeutic strategy for cancer treatment confirmed the potential application of miRNA in oncology. However, the efficiency of a single miRNA might be limited, and combination therapy should be considered. The novel drug delivery carriers should be designed to cross the interstitial barrier, increase local drug concentration, improve therapeutic effect, and reduce side effects. However, miRNAs could regulate gene networks involved in multiple signaling pathways, and the following risks should be considered for clinical application of miRNA-based therapy: (1) whether other mechanisms may lead to anti-tumor activity or toxic side effects, (2) possible immunostimulatory effects, (3) off-target effects, (4) non-specific inflammatory effects of miRNAs. Therefore, further understanding of the mechanisms of miRNAs in pancreatic cancer and the optimization of miRNA vectors provide great promise for developing new treatment strategies against pancreatic cancer.

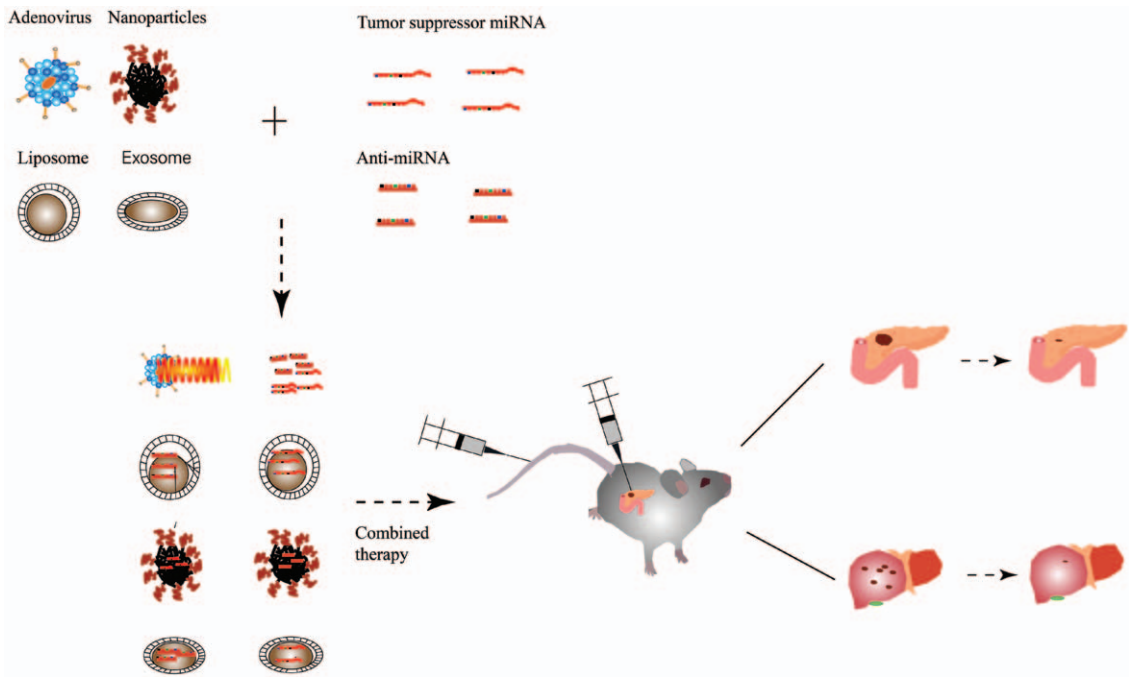

Figure 1: Current targeting of miRNAs with different vectors for inhibiting the progression and metastasis of pancreatic cancer. miRNAs: MicroRNAs.

Conflicts of interest

None.

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