Pancreatic cancer associated micro-RNA

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Abstract. Pancreatic cancer, known as the king of cancer, is a common malignant tumor of digestive tract, with a high degree of malignancy, difficult diagnosis and treatment, and a 5-year survival rate1%, is one of the malignancies with the worst prognosis. Therefore, there is an urgent need for better methods to improve the diagnostic accuracy and better prognosis of pancreatic cancer. Targeted therapy and accurate monitoring of prognosis is one of the key topics of research. Since 2004, when the relationship between micro-RNA and cancer was first revealed, there has been a great deal of interest in the research of micro-RNA. Related categories have been identified as being associated with other cancers, such as lung cancer, and drugs that use micro-RNA to treat cancer have emerged, but only during clinical trials. In this review, we will discuss the relationship between micro-RNA and pancreatic cancer and specifically elaborate microRNA-125a-5p、microRNA-125b、microRNa-423-3p、microRNa-let-7a. At the same time, we summarize the difficulties in using microRNA for targeted therapy and the current clinical situation.

Keywords: Pancreatic cancer, micro-RNA, targeted therapy.

1. Introduction

Pancreatic cancer is a common malignant tumor of digestive tract with a high degree of malignancy. About 90% of pancreatic cancer is ductal adenocarcinoma originating from the glandular epithelium. Diagnosis and treatment are difficult, and the 5-year survival rate. 1%, one of the worst prognosis of malignancies. Early diagnosis of pancreatic cancer is not high, surgical mortality is high, and the cure rate is low. Its morbidity and mortality rates have increased significantly in recent years. At present, the relevant auxiliary examination can mainly be used to diagnose pancreatic cancer by the enhanced examination of thin CT and the examination of tumor markers CA199 and CA242, but the accuracy is low. Abnormalities of tumor markers are often deviated. For example, in actual cases, there will be clinical manifestations of cancer and pathological sections showing tumor cells, but no abnormality of tumor markers. In addition, pancreatic cancer does not infiltrate pancreatic tissues in the early stage, and its location is deep and difficult to detect when palpated. It can be seen that the inaccuracy of examination and diagnosis is also the reason why pancreatic cancer is not easy to find and poor prognosis. Therefore, we need a more accurate and convenient factor to better diagnose and evaluate the prognosis of pancreatic cancer. At present, the treatment of pancreatic cancer is mainly combined with immunotherapy and targeted drugs. Chimeric antigen receptor T cell (CAR-T) immunotherapy is one of the major immunotherapies. This approach has been successfully used in the treatment of hematological malignancies, and in recent years, many researchers have attempted to apply CAR T in the treatment of pancreatic cancer. For hematological tumors, CAR T cells can directly contact tumor cells after entering the blood. But pancreatic cancer, as a solid tumor, is heterogeneous and its histological characteristics prevent CAR T cells from entering the tumor, so it is difficult to completely remove the tumor. Moreover, heterogeneity may lead to different surface antigens in different individuals and tumor cells, so it is difficult to use CAR T to treat solid tumors.

As studies have shown that microRNA has specific expression in various cancers, MicroRNA can also be found to be of significance in the diagnosis and treatment of pancreatic cancer. MicroRNA (miRNA) is a class of non-coding single-stranded RNA molecules encoded by endogenous genes with a length of about 22 nucleotides, which are highly conserved in evolution and play a regulatory role after transcription in vivo. It can induce degradation or translation inhibition of target mRNA by pairing with specific bases of target miRNA, and is a regulator of post-transcriptional gene expression.

[1] There are significant differences in miRNA levels in different tissues and at different developmental stages, and the expression pattern of miRNAs is differentiated in phase and timing, suggesting that miRNAs may be involved in regulating gene expression and can fine-regulate the expression of a gene through the combination of several miRNAs. Therefore, it is of great significance. In 2004, Calin et al. proposed that Mir-15a and Mir-16 were down-regulated in about 65% of patients with B-cell chronic lymphocytic leukemia, which first revealed the correlation between miRNA and tumor. In the 20 years since the discovery that micro-RNA may be associated with cancer, abnormal expression has been found in a variety of cancers, including lung cancer, stomach cancer and skin cancer. In recent studies, the expression regulation of miRNA can affect the proliferation, differentiation, migration and apoptosis of tumor cells. There are two main mechanisms of action. When miRNA is fully complementary to target gene, its mode of action is to directly target and cut miRNA. This mode of action is similar to that of siRNA; Incomplete binding inhibits translation without affecting the stability of miRNA. [2]

In this review, we discuss the mechanism of miRNA's role in pancreatic cancer, and further summarize the role of miRNA and related proteins in pancreatic cancer, so as to achieve early detection and treatment as much as possible, which will greatly improve the prognosis of pancreatic cancer.

2. Pancreatic cancer associated micro-RNA

Abnormal microRNAs are expressed in both pancreatic intraepithelial neoplasia and pancreatic intraepithelial neoplasia. The following lists some specific microRNAs that act on pancreatic cancer by regulating related proteins.

2.1. miRNA-125a-5p

The abnormal expression of miRNA was initially found to be related to immune dysfunction in patients with lupus erythematosus. [3] Low expression of mirNA-125A-5P can directly and negatively regulate the expression of klF13, the main transcription factor secreted by T cells promoting RANTES, thereby reducing the level of T cells producing the inflammatory chemokine RANTES, and thus affecting human immune function, which has been found in lung cancer in recent years. The specific action mode is shown in Figure 1.



Figure 1. Low mirNA-125A-5P expression reduces T cell production of the inflammatory chemokine RANTES.

The abnormal expression of miRNA-125A-5P is significant in the regulation of inflammation after head and neck squamous cell carcinoma and spinal injury, and it is also significant in the abnormal expression of mirNA-125A-5P in pancreatic cancer. Pan Lu juan et al conducted relevant studies on the effect of mirNA-125A-5P on the expression of caspase-8 in subcutaneous transplanted tumor cells of pancreatic cancer by using Western-Blot and other related detection. [4] miRNA-125A-5P can promote cell apoptosis by promoting the expression of Caspase-8, and then play the role of inhibiting the growth of cancer cells Caspases. Caspases are a class of proteases containing cysteine residues. As the main mediators of apoptotic cell death, Caspases are divided into initiator effectors and inflammatory mediators according to their executive functions. Apoptotic initiator factors trigger apoptotic cascade reactions after being activated by apoptotic signals Tumor necrosis factor (TNF) is one of the main drug pathways of cell apoptosis. TNF binds to its cyclocarboxylic acid ligand to stimulate receptor aggregation, in which death domain protein (FADD) binds to Procaspase-8 to form

the death-inducing signal complex (DISC), which ultimately leads to the activation of procaspase-8, which is completed Studies have confirmed that caspase-8 expression is down-regulated in pancreatic cancer, thereby affecting apoptosis and promoting tumor cell growth. The specific action mode is shown in Figure 2.

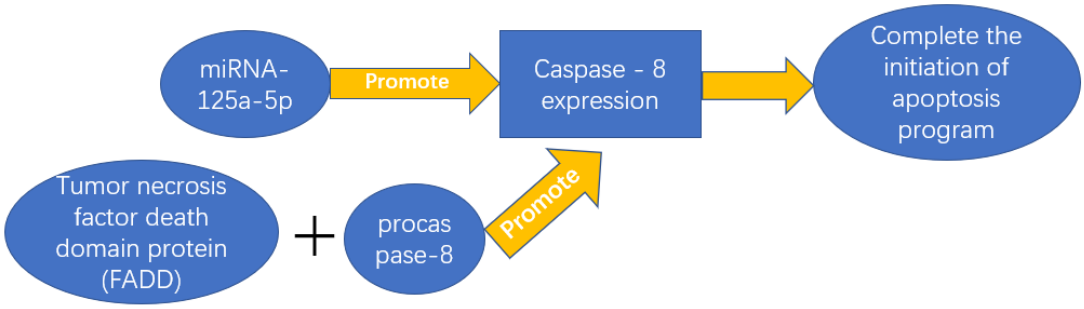


Figure 2. Expression relationship between mirNA-125A-5P and Caspase-8.

2.2. MicroRNA-125b

MicroRNA-125b has attracted much attention in recent years because of its abnormal expression in various cancers such as osteosarcoma and liver cancer. Currently, microRNA-125B in pancreatic cancer can regulate the invasion ability of pancreatic cancer cells through two pathways.

2.2.1 MicroRNA-125b and BAK1

Microrna-125b is highly expressed in pancreatic cancer tissues and inhibits the mitochondrial apoptosis pathway by down-regulating the expression of apoptotic gene BAK1, thus inhibiting the apoptosis of pancreatic cancer cells. [5] Moreover, microRNA-125B decreased the antitumor drug sensitivity of pancreatic cancer cells and increased the pancreatic cancer cells' ischemia tolerance, resulting in a decreased BAK effect Killer (killer) gene is a pro-apoptotic gene in the Bcl-2 gene family. The transcript forms a dimer with Bcl-2XL, a gene product of Bcl-X, a homologue of Bcl-2 (as shown Figure 3), thereby promoting the effect of apoptosis Studies have shown that Bcl-2 can enhance cell resistance to most DNA damage factors and inhibit target cell apoptosis induced by most chemotherapeutic drugs, but it can not inhibit cell damage caused by these factors. Similarly, it does not promote DNA repair. The p53 protein is an important molecular sensor in DNA damage. Bcl-2 inhibits p53 mediated apoptosis, but it does not inhibit p53 translocation into the nucleus or p53 mediated growth stagnation, which prevents the signal that activates apoptosis from reaching its target molecule after DNA damage Bcl-2 was highly expressed in pancreatic cancer tissues. Bcl-2 protein expression was negatively correlated with P53 protein expression.[6]

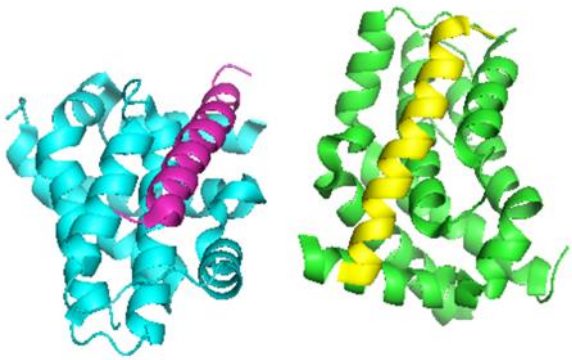


Figure 3. BAK dimers with bcl-2XL, a gene product of bcl-2 homolog Bcl-X.

2.2.2. MicroRNA-125b and PC1

Xu Weixian et al. constructed mir-125b overexpression vector and blank vector to transfect PC cell line Panc-1 cells, and evaluated the change of invasion ability by scratch experiment and

Transwell experiment.[7] Western blot was used Blot analysis of the changes of emT-related proteins e-cadherin and Vimentin showed that Mir-125b regulates invasion ability by affecting the expression of EMT-related proteins such as cadherin E and Vimentin V in PC cells Overexpression of Mir-125 B significantly increased e-cadherin, while decreased expression of Vimentin, inhibited cell epithelialization, and possibly decreased cell invasion ability , as shown in Figure 4. E-cadherin: also known as epithelial cadherin and CD324, is a calcium-dependent cell adhesion molecule consisting of five repetitions of cadherin in the extracellular domain, a transmembrane domain and an intracellular domain that binds p120-conjugate protein and β -conjugate protein It distributes in various epithelial cells of human and animal, participates in cell-to-cell adhesion, and plays an important role in maintaining cell polarity and integrity. Studies have found that e-cadherin is underexpressed in many types of cancer cells, such as lung cancer and gastric cancer, and the low expression of this protein can promote the invasion and metastasis of cancer cells Qin Yi et al. proved by various methods that low expression of intracellular E-cadherin can transform the glucose metabolism pattern and promote the ability of tumor cells to absorb glucose and secrete lactic acid Overexpression of e-cadherin can down-regulate the expressions of key metabolic regulators C-Myc and HIF1α, inhibit the ability of PENC-1 cells to absorb glucose and secrete lactic acid, and significantly down-regulate the expressions of four key genes involved in glycolysis Therefore, it was suggested that e-cadherin could negatively regulate the glycolysis effect of PANC-1 cells, thus regulating the invasion ability of panc-1 cells.[8]

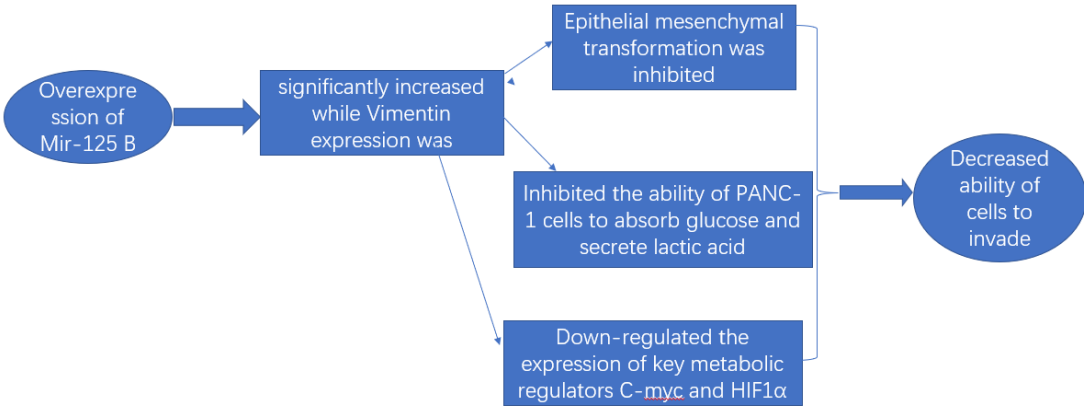


Figure 4. Changes in cell invasion ability induced by mir-125b acting on e-cadherin.

2.3. MicroRNA-423-3p

2.3.1 miRNA-423-3p and Hedgehog (Hh)

miRNA-423-3p was initially proposed to be highly expressed in hepatitis B patients, and was proposed to be used as an indicator of prognosis. In recent years, studies have proposed that SUFU is the main target of Mir-423-3p, and inhibition of Mir-423-3p expression can also inhibit SUFU and significantly reduce apoptosis of drug-resistant cells.[9] As a key factor of Hedgehog (Hh) signaling pathway, SUFU is highly expressed in pancreatic cancer proteins. Hedgehog (Hh) signaling pathway plays an important role in embryonic development, maintaining the dynamic balance between cell proliferation and apoptosis, tissue damage and repair, and the occurrence and development of various malignant tumors In a variety of cancers, such as skin cancer, breast cancer, lung cancer and other cancers of the digestive tract, Hedgehog (Hh) signaling pathway is highly active. Key factors in Hh signaling pathway include Shh Smo SUFU Glil1 Gli2 and Gli3,as shown in Figure 5 , a large number of key factors in Hh signaling pathway were found to be positively expressed in pancreatic cancer. Ma Dan et al. analyzed the expression of key factors in the surgically removed pancreatic cancer tissues of 38 cases, and the specific results were shown in Table 1. [10]In Hh signaling pathway, SUFU Gili1 and Gili1 can interact with each other to jointly regulate the metastasis of cancer cells, as shown in the Figure 6.

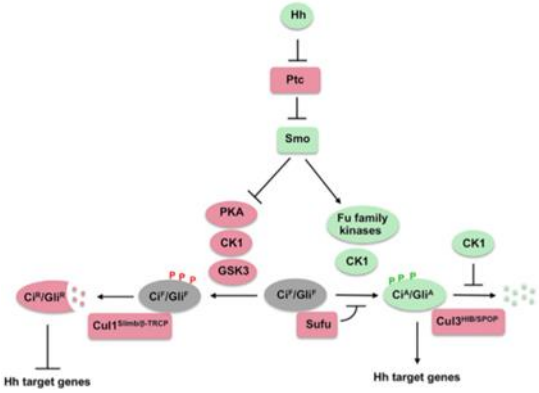


Figure 5. Key factors in Hedgehog (Hh) signaling pathway.

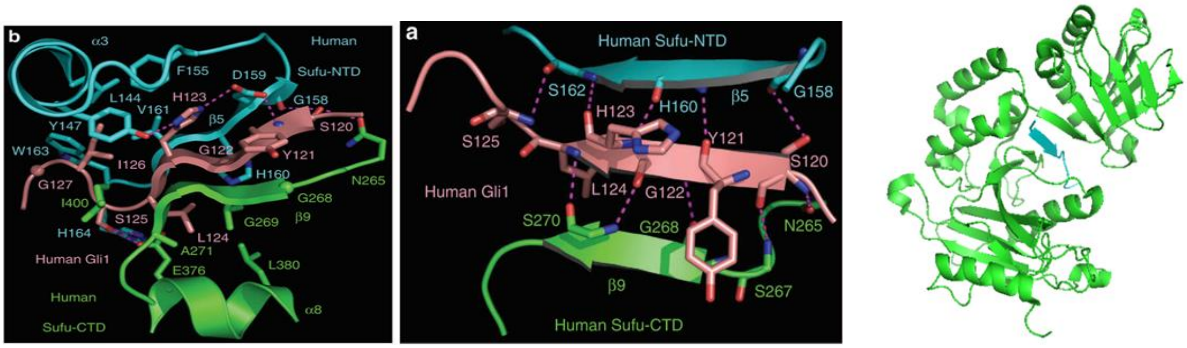


Figure 6. Interaction between SUFU and Gili1. a shows the interaction between the main chain of SUFU and Gili1, b shows the interaction between the side chain.

Table 1. Expression rates of key factors in 38 cases

key factors	Expression rates
Shh	86.8%（33/38）
Glil	52.6%（20/38）
SUFU	68.4%（26/38）
TAK1	55.3%（21/38）、
P-TAK1	52.6%（20/38）

2.3.2 miRNA-423-3p and ISG15

Wang Liang explored the regulation of microrNA-423-3p on the expression levels of ISG15 and PD-L1 in PC cells by double luciferase reporter gene experiment and QRT-PCR Western blot method, and carried out relevant experiments reflecting the impact of Mir-423-3p on invasion.[11] It is concluded that Mir-423-3p can target the 3 UTR of ISG15 and thus down-regulate ISG15. The down-regulation of ISG15 pathway reduces the expression of PD-L1 in PC, thus inhibiting the proliferation and invasive metastasis of PC cells and playing a tumor suppressive role in PC , as shown in Figure 7. ISG15 is a ubiquitin-like protein produced under the stimulation of type I interferon. Its molecular weight is about 15-kDa, and it can covalously modify the target protein through enzyme cascade reaction, thus playing a biological function In addition to binding potential target proteins to form binding forms, ISG15 can also exist in cells in a free form, and ISG15 and ISG transformation are involved in a variety of key cellular processes, including protein translation, autophagy, DNA

repair and immune regulation, which are involved in the regulation of cancer and immune diseases Current studies have revealed that extracellular free ISG15 may act as a supportive factor of tumor stem cells and enhance phenotypic factors of tumor stem cells, thus playing a carcinogenic role in pancreatic ductal adenocarcinoma. However, the specific mechanism of ISG15 and ISG transformation remains to be clarified.[12]

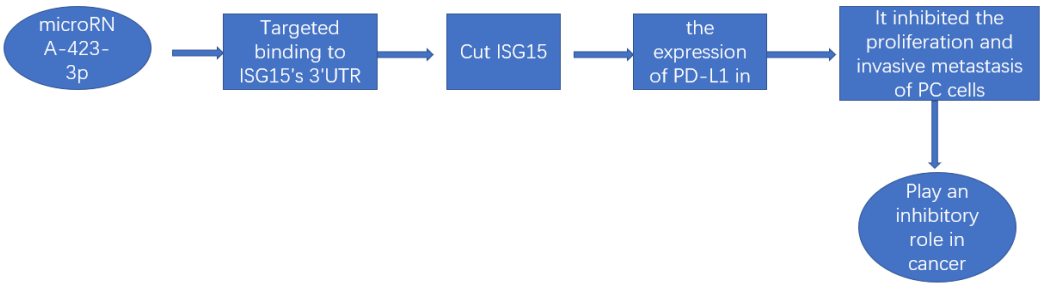


Figure 7. MicrorNA-423-3p plays a tumor suppressive role by regulating the expression of ISG15 and PD-L1.

2.4. miRNA let-7a

MiRNA let-7A in gastric cancer was initially determined by fluorescence quantitative PCR, and it was suggested that miRNA let-7A might have abnormal expression in gastric cancer, which was closely related to the development of gastric cancer. In recent years, it has been found that the expression of leT-7 is down-regulated in a variety of tumors, such as lung cancer and cervical cancer. In normal tissues and organs, leT-7 is normally transcribed, processed and bound to the complementary site of target mRNA, and inhibits gene expression by inhibiting protein translation or changing the stability of mRNA. MiRNA let-7A regulates the invasion and metastasis of cancer cells in various forms, and studies have found that miRNA Let-7A can negatively regulate its target protein Ras. Let-7 can be used as a potential drug for the diagnosis and treatment of lung cancer.

MAO Xingbo et al. explored the low expression of miRNA let-7A in pancreatic cancer tissues by using QT-PCR, and found that there was a significant statistical difference compared with normal adjacent tissues. [13] The relative expression level of miRNA let-7A in cancer tissues was different in different TNM stages and whether lymph node metastasis was detected, and the expression level was different in different genders and ages MiRNA leT-7A is a highly conserved miRNA, and its fragile loci are prone to increase chromosome fragments or lose gene mutations when tumors occur, thus leading to significant changes in LET-7. It is currently believed that leT-7 may bind to the 3UTR of HMGA2 miRNA, resulting in the destruction or disappearance of the 3UTR of HMGA2 miRNA, and then inhibit the expression of HMGA2 miRNA, thus inhibiting carcinogenesis. The mechanism is shown in the Figure 8. HMGA2 has three characteristic DNA binding domains. When it binds to at-rich regions of DNA in the nucleus, the morphology and structure of DNA molecules will change correspondingly, due to the structural differences or length differences of the DNA sequences to be bound HMGA2 is only expressed in early embryonic tissues, and is almost unexpressed or low expressed in healthy mature tissues or cells. However, HMGA2 is highly expressed in almost all tumor tissues By analyzing the expression of HMGA2 in normal pancreatic tissues and that in pancreatic cancer tissues, Wang Yunliang et al. found that HMGA2 was highly expressed in pancreatic cancer tissues, with statistical significance but unclear mechanism, which was not mentioned in relevant literatures at home and abroad.[14]

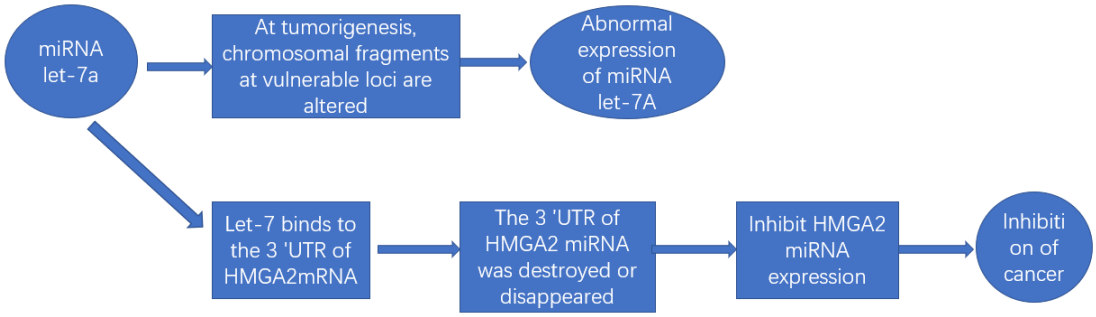


Figure 8. Mechanism of action between miRNA let-7A and cancer.

The above miRNA and protein associations and interactions were summarized in Table 2.

Table 2. Summary of miRNA and protein associations and interactions

miRNAs	Effect of protein	mechanism of action			Results
miRNA-125a-5p	Caspase-8	Promoting caspase-8 protein expression to complete the initiation of apoptosis			Promotes apoptosis
miRNA-125b	BAK1	The mitochondrial apoptosis pathway was inhibited by down-regulating the expression of apoptotic gene BAK1.			Inhibit apoptosis
	E-cadherin	Epithelial mesenchymal transformation was inhibited	Inhibited the ability of PANC-1 cells to absorb glucose and secrete lactic acid	Down-regulated the expression of key metabolic regulators C-myc and HIF1α	Decreased ability of cells to invade
microRNA-423-3p	SUFU	Targeting acts on SUFU and affects Hedgehog (Hh) signaling			Inhibit apoptosis
	ISG15	ISG15 is down-regulated by targeting to 3'UTR of ISG15, and the down-regulation of ISG15 pathway reduces pD-L1 expression in PC			Inhibited the proliferation and invasive metastasis of PC cells,
miRNA let-7a	HMGA2	Binding to the 3 'UTR of HMGA2miRNA results in destruction or disappearance of the 3' UTR of HMGA2miRNA, and inhibits the expression of HMGA2miRNA			Inhibition of cancer

3. The application of micro – RNA

3.1. Research on microRNA therapy

3.1.1 Existing technologies

Currently, molecular drug design based on microRNA is still in its infancy. Studies mainly focus on the simulation of microRNA to enhance its effect on target genes, or the design of small molecule substances targeting microRNA to antagonize the effect of microRNA. Such as microRNA antisense oligomer (deoxy) nucleotides(anti-microRNA oligonucleotides, AMOs) and microRNA antagonistic molecules (antagomirs). AMOs can complement both mature microRNA and its precursors, and can influence its translation process by hybridizing with complementary chains through base pairing. But unmodified DNA oligonucleotides are degraded by enzymes in the body, rendering them useless. So AMOs was chemically modified to improve its stability and affinity. MicroRNA antagonists, antagomirs, have successfully inhibited microRNA action in cultured cells, but have yet to be studied in animal models. It covalently binds to cholesterol at the 3' end and complements mature target microRNA sequences. The drug was administered intravenously, successfully silencing microRNA expression in liver, lung and bone marrow, and the effect lasted for more than a week. [15]

3.1.2 Research on pancreatic cancer

Many studies have reported that the drug resistance and insensitivity of pancreatic cancer chemotherapy drugs are related to the expression of some miRNA in pancreatic cancer growth. Conti et al. proved that the expression levels of Mir-10 and Mir-155 in serum were related to the sensitivity and drug resistance of gemcitabine, and it was suggested to detect the levels of these two miRNAs in serum before chemotherapy. Different miRNA expression levels had different chemotherapy effects. Exploring the relationship between miRNA and traditional treatment of pancreatic cancer can open a new breakthrough for the treatment of pancreatic cancer. The combination therapy of miRNA and chemotherapy drugs is also a potential and promising research direction, which can not only target multiple signaling pathways with the advantages of miRNA, but also exert the cytotoxic effect of anti-cancer drugs Reduction of chemotherapy resistance in pancreatic cancer cells.[16]

3.2. Difficulties in implementing micro-RNA targeted therapy

Targeted therapy for miRNA is a new treatment method, which can inhibit the expression of proto-oncogenes of pancreatic cancer by re-expression or expression inhibition of miRNA. The targeted therapy of cancer using miRNA alone is still in clinical trials. At present, the regulatory expression of miRNA has been achieved, but the application of miRNA therapy is relatively lagging behind, which is mainly due to the immature research on the anti-tumor targeted delivery mechanism of miRNA Because therapeutic miRNAs must pass through multiple biological barriers, such as tumor microenvironment, in order to achieve targeted regulation, the stability of drugs will be reduced in the process of passage Based on this, developed more delivery systems in recent years, such as nanoparticle delivery carrier, recombinant viral vector, secrete body outside the delivery carrier, carrier virus-like particles and charge between based on stem cells (MSC) delivery systems and so on, as shown in Figure 9 Nanoparticles can be coupled with the antibody molecules and increase the drug to the tumor cell specificity recognition and killing ability But further research is needed to develop more efficient delivery systems for better clinical use.[3]

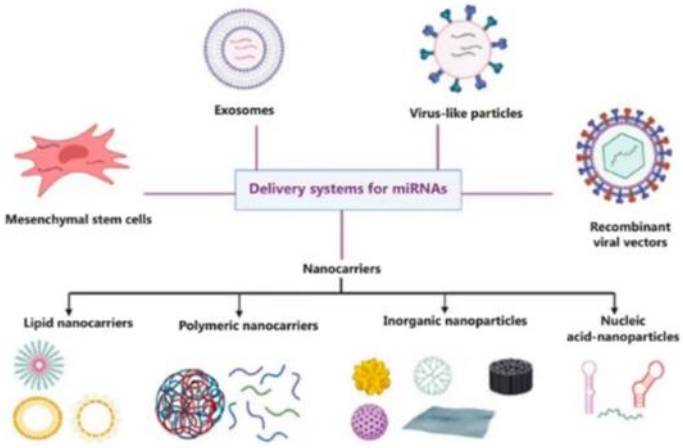


Figure 9. Main miRNA delivery systems.

4. Conclusion

In recent years, the incidence of pancreatic cancer has been increasing, but no breakthrough has been made in the pathogenesis, diagnosis and treatment of pancreatic cancer. MicroRNA, as a research hotspot, has been proved to play a relevant role in the proliferation, invasion and metastasis of a variety of tumors. There are also a variety of microRNA with abnormal expression in pancreatic cancer, which can be used to diagnose pancreatic cancer and realize targeted therapy or combination therapy to improve the therapeutic effect. With the continuous improvement of technological means, the research on miRNA has gradually shifted from the basic direction to the direction of clinical application, and more and more studies have focused on the application of vector-mediated microRNA delivery in cancer treatment. MicroRNA has diversity, and it is difficult to achieve specific targeting. However, at the same time, it can be used to break the previous single-target drugs and achieve multiple targets. For existing antagonists, effective vectors and chemical modifications should be considered before miRNA drugs are applied to the clinic. At present, the biggest problem facing microRNA-based drug development is to find appropriate drug delivery routes and drug targeting, which still needs further exploration and practice.

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