Review Article

Research progress on microRNAs as molecular markers in pancreatic cancer: a narrative review

Rui-Biao Fu[1#^], Xi Chen[1#^], Yan Chen[1^], Qing-Huang Ye[1^], Bin Yang[1^], Qian Shao[2^], Jin-Hui Zhu[1^]

[1]Department of General Surgery, Second Affiliated Hospital Zhejiang University School of Medicine, Hangzhou, China; [2]Department of Surgery, Ningbo Women's and Children's Hospital, Ningbo, China

Contributions: (I) Conception and design: All authors; (II) Administrative support: JH Zhu, Y Chen; (III) Provision of study materials or patients: RB Fu, X Chen, JH Zhu; (IV) Collection and assembly of data: RB Fu, X Chen; (V) Data analysis and interpretation: RB Fu, X Chen, JH Zhu, QH Ye; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to the work.

Correspondence to: Jin-Hui Zhu, MD, Professor. Department of General Surgery, Second Affiliated Hospital Zhejiang University School of Medicine, Hangzhou 310009, China. Email: 2512016@zju.edu.cn.

Background and Objective: The incidence and mortality of pancreatic cancer (PC) have increased in recent years. The current status of PC diagnosis and treatment remains grim in clinical practice because the commonly used early screening tools are not sufficient. Improving the early detection of PC and strengthening standardized comprehensive treatment remain the focus of PC research. Many studies have shown that micro RNAs (miRNAs) play an important role in the occurrence, development, and treatment of PC. It is expected that miRNAs will become new molecular markers of PC.

Methods: We extracted and compiled useful information from the PubMed database that met our criteria for analyzing PC diagnosis, treatment, and prognosis.

Key Content and Findings: In this narrative review, we summarize the mechanism of some miRNAs in the occurrence and development of PC and review them as potential markers for the diagnosis, treatment, and prognosis of PC. The function of miRNAs in PC has great potential in studying the pathogenesis of PC. The discovery of many important oncogenic miRNAs and their downstream targets will bring new ideas and research paths for the diagnosis and targeted therapy of PC.

Conclusions: MiRNAs are expected to provide novel ideas and research directions for the diagnosis and targeted treatment of PC. However, more patient data and clinical trials are needed before miRNAs can become novel molecular markers for PC.

Keywords: Pancreatic cancer (PC); micro RNAs (miRNAs); molecular markers

Submitted May 25, 2022. Accepted for publication Jul 12, 2022.
doi: 10.21037/jgo-22-577
View this article at: https://dx.doi.org/10.21037/jgo-22-577

Introduction

Pancreatic cancer (PC) has a high mortality rate (1). Despite its relatively low incidence (it is the 10th most common cancer among all cancers), it is the 4th most common cause of cancer-related death in most developed countries (1,2). Statistics from the China National Cancer Center have confirmed that PC is the 8th most common malignant tumor in Chinese men and the 6th leading cause of death from malignant tumors among people living in

^ ORCID: Rui-Biao Fu, 0000-0003-1962-3315; Xi Chen, 0000-0001-8452-2006; Yan Chen, 0000-0002-8627-8825; Qing-Huang Ye, 0000-0002-8566-1507; Bin Yang, 0000-0002-3942-0892; Qian Shao, 0000-0002-1002-380X; Jin-Hui Zhu, 0000-0003-0136-1150.

Table 1 The search strategy summary

Items	Specification
Date of search	January 1st, 2022
Databases and other sources searched	PubMed database
Search terms used	"Pancreatic cancer"; "MicroRNA"; "Molecular markers"; "Diagnosis"; "Treatment"; "Prognosis"
Timeframe	December 1, 1997 to September 26, 2021
Inclusion and exclusion criteria	Inclusion criteria—Study type: basic and clinical medical research. The articles were limited to full-text publications in English. No specific exclusion criteria
Selection process	The articles were independently selected by the first authors, Rui-Biao Fu and Xi Chen, and included in the review after agreement was reached following several consultations and discussions with the co-authors
Any additional considerations, if applicable	N/A

large cities in China (3,4). The clinical features of PC are not significant. PC has many symptoms, including jaundice, back/abdominal pain, loss of appetite, and weight loss (5). Additionally, PC is extremely aggressive, metastatic, and chemotherapy-resistant (6). Even at an early stage, local invasion and distant metastasis are often clinically observed. Surgery, radiation, chemotherapy, and some marginally effective targeted therapies are among the conventional treatment choices for people with PC.

Since the incidence and mortality of PC have increased in recent years, a better understanding of PC is urgently required. A greater knowledge of the disease's pathophysiology will allow for the earlier identification and development of viable therapies. Micro RNAs (miRNAs) are endogenous short non-coding RNAs that control gene expression and play an important role in the onset, development, and therapy of different malignancies. Different levels of miRNAs expression can be detected in the blood of patients. A study has confirmed that abnormal expression of some miRNAs is not only related to the type of cancer, but also to its stage of development (7). These findings enable miRNAs to become non-invasive molecular biomarkers for PC detection, prediction and monitoring of therapeutic effect. Based on the structure and molecular characteristics of miRNAs, combined with the regulatory mechanism of miRNAs in PC, this paper describes the role of miRNAs in the pathogenesis, development, diagnosis, treatment and prognosis of PC. We believe that miRNAs are expected to be used in the diagnosis, prognosis and targeted therapy of PC through the analysis of miRNA differentiation and expression profile. We present the following article in accordance with the Narrative Review reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-577/rc).

Methods

We searched the PubMed database for literature on the miRNAs and molecular markers of PC published in the past 10 years, and selected classified, and summarized the relevant literature after discussions among the authors. The specific search strategy is listed in *Table 1*.

MiRNAs

In recent years, many studies have shown that miRNAs can be used as potential biomarkers of PC (7-9). MiRNAs are a class of non-coding single-stranded RNA molecules encoded by endogenous genes, about 22 nucleotides in length, which participate in the post-transcriptional regulation of gene expression and regulate cell growth, proliferation, differentiation, apoptosis and other important biological functions (4). In an organism, miRNAs are synthesized by miRNA genes through a complex process (see at *Figure 1*). The targeting characteristics of miRNAs are classified into groups depending on the identity of their extended seed region (miRNA nucleotides 2–8) (11). MiRNAs are a kind of non-coding RNA that control gene expression by degrading mRNA or inhibiting translation (12). MiRNAs play 2 major roles in carcinogenesis, and have

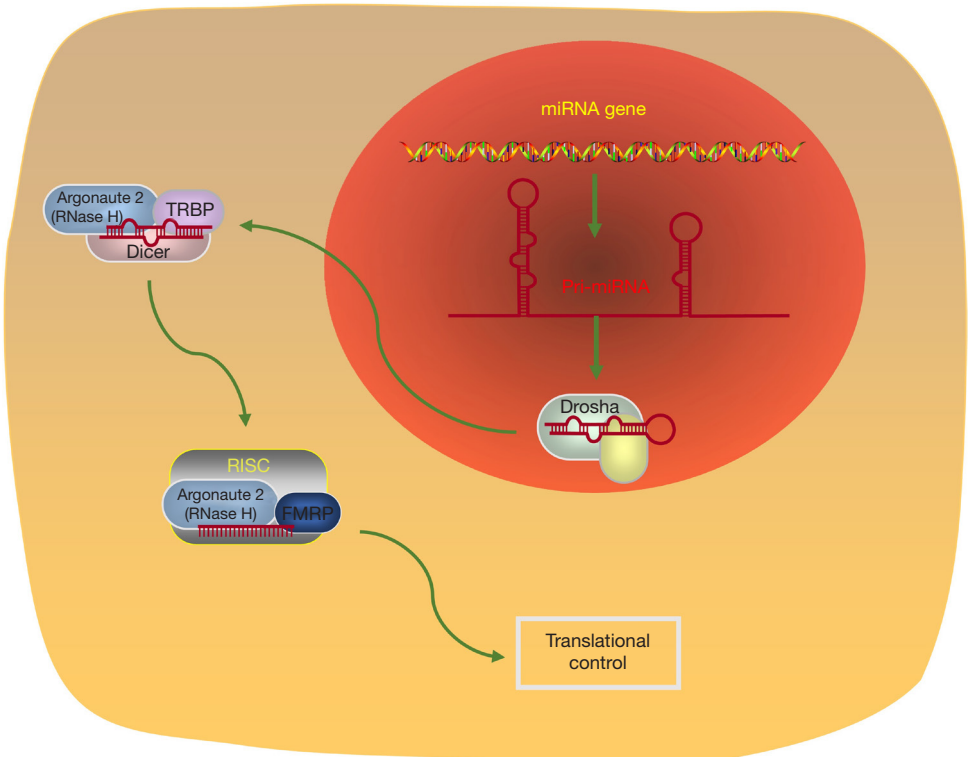

Figure 1 The process of miRNA biogenesis. First, pri-miRNA is synthesized in the nucleus by the action of RNA polymerase II using miRNA genes as templates. Pri-miRNA is cleaved into miRNA double strands by Drosha RNase III and Dicer RNase III. Next, the RNA-induced silencing complex incorporates activated miRNA. After the above transcription and processing in the nucleus, the double-stranded miRNA moves to the cytoplasm and dissociates into mature single-stranded miRNA. Mature miRNAs play a role in mediating the silencing of target gene protein expression by binding to RNA inducers, thus controlling cell growth, development and apoptosis (10). miRNA, microRNA; TRBP, HIV-1 Tar RNA binding protein; Dicer, Dicer RNase III; RISC, RNA-induced silencing complex; FMRP, Fragile X mental retardation protein.

inhibition and promotion effects (13). Normally, these 2 effects are in a state of balance; However, when this balance gets out of control, unregulated miRNAs (i.e., excessively upregulated or downregulated miRNAs) cause the body to lose control over the formation of specific tumors. This loss of control usually refers to the activation of oncogenes and the disorder of apoptosis (14).

MiRNAs are widespread and stable in biological body fluids, so they are ideal molecular markers for the rapid, non-invasive, and inexpensive detection and diagnosis of diseases. A study has shown that some PC-related miRNAs present stably in tissues, blood, and feces, and can be quantified in very small sample sizes (15). PC tissues from various sources, such as fine-needle biopsies, fresh frozen tissues, and formalin-fixed paraffin-embedded tissues, are now being employed for miRNA mapping research. For example, a miRNA microarray examination of PC tissue collected through fine-needle aspiration biopsy revealed that 158 miRNAs were improperly expressed in PC tissue as compared to healthy pancreatic tissue. The researchers chose 8 miRNAs for further analysis, 5 of which were highly expressed (miR-21, miR-27a, miR-146a, miR-200a, and miR-196a), and 3 of which were found to be lowly expressed (miR-217, miR-20a, and miR-96) in PC tissues (16).

The findings on the miRNA mapping of PC tissues confirmed the importance of miRNAs in the development of PC. However, due to its invasive nature and high costs, fine-needle biopsy is a major impediment to the use of miRNAs as markers in the detection of PC. If aberrantly expressed miRNAs can be detected in the peripheral blood of patients with PC, miRNAs will have a better chance of becoming PC biomarkers. A study showed that serum

Table 2 A summary of the significant upregulated and downregulated miRNAs, and their relative roles in PDAC carcinogenesis

miRNA	Express status	Target genes/signaling pathways	Role in PC	Reference
miR-573	Downregulated	TSPAN1	Inhibition of PC cell proliferation, colony formation, migration, and invasion, as well as tumor growth suppression *in vivo*	(8)
miR-139	Downregulated	*RalB*	Suppression of PC cell growth and metastasis	(20)
miR-122-5p	Downregulated	CCNG1	Proliferation, migration, and invasion are decreased *in vitro*, and tumorigenesis is prevented *in vivo*	(21)
miR-505	Downregulated	HK2	Inhibition of cell proliferation, invasion, sphere formation, glucose consumption, and lactate production	(22)
miR-125b	Upregulated	Txnip	Promotion of proliferation and migration	(23)
miR-132-3p	Upregulated	Rb1	Promotion of PC cell growth	(24)
miR-543	Upregulated	*STK31*	Promotion of PC cell growth	(25)
miR-361-3p	Upregulated	B-cell Translocation Gene 2	Inhibition of cell proliferation, migration, and invasion, and stimulation of cell cycle arrest and apoptosis	(26)
miR-217	Upregulated	KRAS	The overexpression of miR-217 in a pancreatic tumor cell line lowers KRAS levels, inhibits cell proliferation, and diminishes the constitutive phosphorylation of the downstream signal transducer protein kinase B	(27)
miR-27a	Upregulated	Sprouty2	Promotion of PC cell growth	(28)

miRNA, micro RNA; PDAC, pancreatic ductal adenocarcinoma; PC, pancreatic cancer; KRAS, kirsten rat sarcoma viral oncogene.

miRNA can be used to distinguish PC patients from chronic pancreatitis patients and healthy individuals (17). Similarly, Schultz *et al.* used whole blood RNA samples in their study and found that 2 diagnostic panels of miRNAs had the potential to differentiate between PC patients and healthy controls (18). Hussein *et al.* detected the expression of miR-22-3p, miR-642B-3p, and miR-885-5p in the plasma of patients with PC and found that the levels of 3 kinds of miRNA in plasma were significantly higher than those in healthy controls, indicating that these related miRNAs in plasma may be used as potential biomarkers in the diagnosis of PC (19). These experiments revealed the possibility of using peripheral blood miRNAs as molecular markers of PC.

Pathogenesis of miRNAs

Research has shown that cytokines and core signaling pathways are primarily involved in miRNA-mediated control (see *Table 2*). Patients with PC had considerably higher levels of MiR-21 in their serum compared with healthy people (29). Abue *et al.* used quantitative real-time polymerase chain reaction (RT-PCR) to detect the expression of miR-21 in the plasma samples of 32 patients with pancreatic ductal adenocarcinoma (PDAC), 12 patients with intraductal papillary mucinous tumors, and 30 healthy controls, and found that the plasma expression levels of miR-21 of these patients were substantially higher than that of healthy controls, and that miR-21 expression was also related to staging, lymph node metastases, and a short survival time (29). Dong *et al.* studied the mechanism by which miR-21 affects the occurrence and development of PC. Specifically, Dong *et al.* selected PC cell line MIAPaca-2 as the research object to explore the mechanism of miR-21 on the crucial modulator of apoptosis, Bcl-2 factor, which mediates apoptosis. The Bcl-2 protein is the coding product of proto-oncogene Bcl-2, which can prevent the release of cytochrome C from mitochondria to the cytoplasm and thus inhibit cell apoptosis. Dong *et al.* found that miR-21 promotes the expression of Bcl-2 protein by binding to the 2 prime untranslated regions of Bcl-2mRNA, which inhibits the apoptosis of MIAPaca-2 PC cells (30). Research has also shown that the inhibition of miR-21 in PC cells decreases the proliferation rate of cancer cells, but increases apoptosis, and that the expression of the tumor suppressor genes programmed cell death 4 (PDCD4) and

Phosphatase and tensin homolog (PTEN) is upregulated in PC patients, which suggests that both may be targets of miR-21 (18,19).

Zhao *et al.* studied the biological activity of serum miR-192a in patients with PADC and evaluated its potential as a biomarker. They found 16 upregulated miRNAs, including miR-192, and 8 downregulated miRNAs in the miRNA expression profiles of human PDAC and neighboring normal pancreatic tissues. According to RT-PCR, the level of serum miR-192 in patients with PDAC was higher than that in PC patients and healthy controls. A further analysis showed that the sensitivity of serum miR-192 in detecting PDAC was 76% and the specificity was 55% (31). In PANC-1 PC cells, the ectopic expression of miR-192 can accelerate cell proliferation and migration, inhibit apoptosis, and shift the cell cycle from the G0/G1 to S phase. A western blot analysis showed that the forced expression of miR-192 in PANC-1 cells lowers the expression of Smad interacting protein 1 (SIP1) and modifies the expression of a collection of cell cycle associated genes (31). Thus, miR-192 overexpression aids in the growth and progression of PC.

The expression of miR-155 is upregulated in the blood of patients with PC, making it a potential marker of PC (32). Liu *et al.* studied the inhibitory effect of miR-155 on the tumor suppressor gene SEL1L (33). The messenger RNA (mRNA) of the SEL1L gene is highly expressed in healthy adult pancreatic tissues (34), and the gene has been shown to have a tumor inhibitory effect (35,36). The expression level of SEL1L mRNA was found to be negatively correlated with the expression of hsa-mir-143, hsa-mir-155 and hsa-mir-223. And after further analysis, it was concluded that hsa-mir-155 inhibited SEL1L in PDAC cells (33). Another study found that miR-155 expression was upregulated in PC tissues, while cytokine signal transduction inhibitor 1 (SOCS1) expression was lower in PC tissues and higher in paracrine tissues. Further, miR-155 expression levels are related to lymph node metastasis and clinical stage, which suggests that miR-155 may regulate PC cell invasion and migration by targeting the SOCS1 signal pathway (36).

MiRNAs as diagnostic markers

Currently radical resection is the only possible cure for PC, and early operation provides patients with a better chance of cure. However, due to the low rate of early diagnosis of PC, only a very small number of patients obtain radical resection at the early stage. The key to changing this situation lies in the use of more sensitive molecular markers of PC and in finding therapeutic approaches other than surgery. As a result, laboratories around the world are searching for molecular markers that can detect PC early and enable a larger proportion of patients to be treated.

According to a study, using miR-27a-3p expression levels in peripheral blood monocytes (PBMCs) to differentiate PC from benign pancreatic/peripancreatic diseases (BPD had a sensitivity of 82.2% and a specificity of 76.7%, while the combined diagnosis of PBMC miR-27a-3p and serum CA19-9 levels is more accurate, with a sensitivity of 85.3% and a specificity of 81.6% (37). Hussein *et al.* showed that the abnormal expression of plasma miR-22-3p, miR-642b-3p and miR-885-5p easily distinguished PC patients from healthy controls (19). Slater *et al.* examined the role of miRNA in screening individuals at risk for familial pancreatitis. Specifically, they analyzed miRNA-21,-155,196a, 196b, and 210 in the serum of transgenic LSL-Kras^{G12D}/+; LSL-Trp53^{R172H}/+; Pdx-1-Cre (KPC) mice to determine whether they could differentiate between different grades of pancreatic intraepithelial neoplasia (mPanIN1-3) or PC, and concluded that the combination of miR-196a and 196b might be a potential biomarker for identifying people at risk of familial pancreatitis (38). Zou *et al.* discovered that mir-192-5p, mir-19a-3p, mir-19b-3p, mir-223-3p, and mir-25-3p were significantly upregulated in serum PC samples, and suggested that they might be used for the early non-invasive detection of PC (39).

MiRNAs as therapeutic markers

In addition to being potential PC biomarkers, miRNAs have shown potential in PC therapy (28,37). Studies have shown the effectiveness of miRNAs in PC treatment. For example, a study showed that the abnormal expression of miRNA is closely related to the occurrence and development of PC. As a result, the reversal of aberrant miRNA expression might be a viable technique for PC prevention and treatment (40). MiRNA-21, a miRNA that has one of the greatest effects on pancreatic ductal carcinoma, has been shown to be significantly increased in patients with PC (41). Zhao *et al.* found that both miRNA-21 and miRNA-221 upregulate and participate in the proliferation, apoptosis, and chemotherapy resistance of PC in small groups of cells with stem cell-like characteristics, and the combination of antisense oligodeoxynucleotides targeting miRNA-21 and miRNA-221 significantly inhibits the growth and metastasis of primary tumors (42). In another study on miRNA-21, researchers used an animal model of pancreatic ductal

carcinoma for the non-invasive tracking of tumor growth. Ultimately, they found that invasive tumors within the animal model stopped growing after miRNA-21 expression in tumor cells was suppressed. Thus, they suggested that the therapeutic administration of miRNA-21 antagonists would be beneficial for PC treatment (43). Nalls *et al.* discovered that the re-expression of miR-34a in human PC stem cells and human PC cell lines after treatment with the demethylation drug 5-aza-29-deoxcytidine (5-aza-DC) and the histone deacetylase inhibitor Vorinostat (SAHA) strongly inhibited cell proliferation, cell cycle progression, self-renewal, epithelial-to-mesenchymal transformation, and invasion (44). Passadouro *et al.* developed a novel treatment method that employed anti-miRNA oligonucleotides (AMOs) against overexpressed miRNAs in PDAC, mediated by a lipid-based nano system, with considerable anti-cancer effectiveness (45). Further, when this anti-cancer gene therapy technique that employed AMOs was combined with modest doses of chemotherapeutic drugs, it had a synergistic and substantial antitumor effect in PDAC cell lines (46).

MiRNAs as prognostic markers

Some miRNAs have been shown to be associated with the aggressiveness of PC and patient survival. In a meta-analysis of 1,471 patients in 17 studies, the upregulation of miRNA-21 had a strong correlation with poor overall survival (OS), disease-free survival (DFS), and progression-free survival, and for patients undergoing adjuvant chemotherapy, the overexpression of miRNA-21 had a considerably great prognostic value and has also been linked to a greater probability of metastatic lymph node involvement and poorly differentiated malignancies (47). Namkung *et al.* performed a microarray analysis on pancreatic tumors in Korea, and obtained 1,733 miRNA expression profiles. MiRNA-574-5p, miRNA-1244, and miRNA-4474-5p were upregulated in expression. MiRNA-574-5p, miRNA-1244, miRNA-145, miRNA-328, miRNA-26b, and miRNA-4321 were correlated with total OS and DFS. Thus, these markers may be used as biomarkers to predict the prognosis of PC patients (48).

Additionally, miRNAs may also play a potential role in predicting the efficacy of the chemotherapeutic drug gemcitabine (48). Another study found that miR-7 was considerably downregulated in PC patients, and that low levels of miR-7 expression were associated with a poor prognosis. Ohuchida *et al.* found that patients with a high expression of miR-142-5p and miR-204 had significantly longer survival than patients with a low expression of miR-142-5p (P=0.0077) and miR-204 (P=0.0054) (49). Similarly, another study found that the postoperative survival rate of patients with elevated miRNA-200c expression was higher than that of patients with lower miRNA-200c expression (50). By combining paired miRNA/mRNA expression data, Vrahatis *et al.* developed an excellent method for capturing a miRNA-mediated signaling pathway (51). Liu *et al.* extracted 10 miRNA-mRNA modules associated with PC on this basis. Ultimately, 6 miRNA-mRNA modules were discovered to have value in predicting PC patient survival (52). Zhang *et al.* established and validated a miRNA set-based pathway predictive signature for PC (miPPSPC) using a gene set variation analysis. The miPPSPC showed that 4 metabolic pathways and 1 oxidative stress route were linked to PC patient survival based on tissue microarray results (53). The cell experiments of Wu *et al.* showed that Mir-221-3p promoted the proliferation, migration, invasion and drug resistance of PC cells, but inhibited apoptosis, which reduced the survival rate of PC patients (54).

Discussion

Based on previous research, the role of miRNAs in PC may help us to reveal the mechanism of pancreatic carcinogenesis in the future. For example, cancer-associated fibroblasts (CAFs) play an important role in the development and progression of PC (55). Studies have shown that miR-15a, miR-16, miR-31, miR-155, and miR-124 can promote the proliferation of CAFs (9). CAFs can provide PDAC cells with metabolic support, including amino acids and lipids, as well as paracrine signaling to promote growth and survival (56). The regulation of miRNAs in PC was a network. In PC, the decreased expression level of miRNAs regulating oncogene formation leads to their overproduction, while the increased level of other miRNAs involved in the regulation of inhibiting gene expression inhibits the formation of these anticancer genes (57). The network promotes PC formation, or is able to restore normal gene expression profiles to halt PC development. MiRNAs have shown great potential in the diagnosis, treatment and prognosis of PC. MiRNAs have proved that they can be used in the diagnosis and prognosis of PC by regulating proto-oncogenes and tumor suppressor genes if we obtain enough MiRNA expression profiles from cancer and normal tissues. By identifying the differentiation

and expression profile of miRNA, we can determine the degree of tumor development and provide the possibility of using corresponding therapeutic approaches. Additionally, some key oncogenic miRNAs have been identified and their downstream targets will provide new ideas and research directions for the diagnosis and targeted therapy of PC. In terms of diagnostic markers, the early diagnosis rate of PC via detection with a single marker is still not sufficiently high; however, the combination of multiple markers improves the accuracy of early diagnosis. In terms of treatment, the existing research results have mainly relied on animal models; thus, there is still a lack of clinical trials. Additionally, to use miRNAs as a mature treatment of PC, we also need to overcome a number of problems, including finding an efficient and accurate precise delivery vector, and the high treatment costs (43). In the field of PC research in the future, the research on miRNAs will focus on miRNA-mediated cytokines and core signaling pathways, as well as the specific mechanism of miRNA promoting drug resistance in PC.

Conclusions

Currently, more extensive patient data, relevant clinical experience, and further studies are needed to verify whether miRNAs can serve as meaningful molecular markers for the early diagnosis, treatment, and prognosis of most PC patients.

Acknowledgments

Funding: This work was supported by the Zhejiang Province Bureau of Health (No. 2020366835), and the Science Technology Department of Zhejiang Province (No. 2020C03074).

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-577/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form. (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-577/coif). All authors report that this work was supported by the Zhejiang Province Bureau of Health (No. 2020366835), and the Science Technology Department of Zhejiang Province (No. 2020C03074). The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work, including ensuring that any questions related to the accuracy or integrity of any part of the work have been appropriately investigated and resolved.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70:7-30.
2. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. CA Cancer J Clin 2016;66:115-32.
3. Ebrahimi S, Hosseini M, Ghasemi F, et al. Circulating microRNAs as Potential Diagnostic, Prognostic and Therapeutic Targets in Pancreatic Cancer. Curr Pharm Des 2016;22:6444-50.
4. Krol J, Loedige I, Filipowicz W. The widespread regulation of microRNA biogenesis, function and decay. Nat Rev Genet 2010;11:597-610.
5. Johnson AM, Wolf S, Xuan M, et al. Index Symptoms and Prognosis Awareness of Patients With Pancreatic Cancer: A Multi-Site Palliative Care Collaborative. J Palliat Care 2021. [Epub ahead of print]. doi: 10.1177/08258597211001596.
6. Longati P, Jia X, Eimer J, et al. 3D pancreatic carcinoma spheroids induce a matrix-rich, chemoresistant phenotype offering a better model for drug testing. BMC Cancer 2013;13:95.
7. Smolarz B, Durczyński A, Romanowicz H, et al. The Role of microRNA in Pancreatic Cancer. Biomedicines 2021;9:1322.
8. Wang L, Gao P, Yuan P, et al. miR-573 suppresses pancreatic cancer cell proliferation, migration, and invasion through targeting TSPAN1. Strahlenther Onkol 2021;197:438-48.
9. Baradaran B, Shahbazi R, Khordadmehr M. Dysregulation

of key microRNAs in pancreatic cancer development. Biomed Pharmacother 2019;109:1008-15.
10. Winter J, Jung S, Keller S, et al. Many roads to maturity: microRNA biogenesis pathways and their regulation. Nat Cell Biol 2009;11:228-34.
11. Bartel DP. MicroRNAs: target recognition and regulatory functions. Cell 2009;136:215-33.
12. Mulholland EJ, Dunne N, McCarthy HO. MicroRNA as Therapeutic Targets for Chronic Wound Healing. Mol Ther Nucleic Acids 2017;8:46-55.
13. Zhang B, Pan X, Cobb GP, et al. microRNAs as oncogenes and tumor suppressors. Dev Biol 2007;302:1-12.
14. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell 2000;100:57-70.
15. Hernandez YG, Lucas AL. MicroRNA in pancreatic ductal adenocarcinoma and its precursor lesions. World J Gastrointest Oncol 2016;8:18-29.
16. Hong TH, Park IY. MicroRNA expression profiling of diagnostic needle aspirates from surgical pancreatic cancer specimens. Ann Surg Treat Res 2014;87:290-7.
17. Johansen JS, Calatayud D, Albieri V, et al. The potential diagnostic value of serum microRNA signature in patients with pancreatic cancer. Int J Cancer 2016;139:2312-24.
18. Schultz NA, Dehlendorff C, Jensen BV, et al. MicroRNA biomarkers in whole blood for detection of pancreatic cancer. JAMA 2014;311:392-404.
19. Hussein NA, Kholy ZA, Anwar MM, et al. Plasma miR-22-3p, miR-642b-3p and miR-885-5p as diagnostic biomarkers for pancreatic cancer. J Cancer Res Clin Oncol 2017;143:83-93.
20. Wang Y, Zheng Y, Chen Q, et al. MicroRNA-139 inhibits pancreatic-cancer carcinogenesis by suppressing RalB via the Ral/RAC/PI3K pathway. Arch Biochem Biophys 2021;704:108719.
21. Dai C, Zhang Y, Xu Z, et al. MicroRNA-122-5p inhibits cell proliferation, migration and invasion by targeting CCNG1 in pancreatic ductal adenocarcinoma. Cancer Cell Int 2020;20:98.
22. Xu Z, Zhang D, Zhang Z, et al. MicroRNA-505, Suppressed by Oncogenic Long Non-coding RNA LINC01448, Acts as a Novel Suppressor of Glycolysis and Tumor Progression Through Inhibiting HK2 Expression in Pancreatic Cancer. Front Cell Dev Biol 2020;8:625056.
23. Wang P, Zheng D, Qi H, et al. Thioredoxin-interacting protein is a favored target of miR-125b, promoting metastasis and progression of pancreatic cancer via the HIF1α pathway. J Biochem Mol Toxicol 2021;35:e22782.
24. Rafat M, Moraghebi M, Afsa M, et al. The outstanding role of miR-132-3p in carcinogenesis of solid tumors. Hum Cell 2021;34:1051-65.
25. Yuan W, Gao H, Wang G, Miao Y, Jiang K, Zhang K, et al. Higher miR-543 levels correlate with lower STK31 expression and longer pancreatic cancer survival. Cancer Med. 2020 Dec;9(24):9632–40.
26. Huang L, Han J, Yu H, et al. CircRNA_000864 Upregulates B-cell Translocation Gene 2 Expression and Represses Migration and Invasion in Pancreatic Cancer Cells by Binding to miR-361-3p. Front Oncol 2020;10:547942.
27. Yang J, Zhang HF, Qin CF. MicroRNA-217 functions as a prognosis predictor and inhibits pancreatic cancer cell proliferation and invasion via targeting E2F3. Eur Rev Med Pharmacol Sci 2017;21:4050-7.
28. Suzuki HI, Katsura A, Mihira H, et al. Regulation of TGF-β-mediated endothelial-mesenchymal transition by microRNA-27. J Biochem 2017;161:417-20.
29. Abue M, Yokoyama M, Shibuya R, et al. Circulating miR-483-3p and miR-21 is highly expressed in plasma of pancreatic cancer. Int J Oncol 2015;46:539-47.
30. Dong J, Zhao YP, Zhou L, et al. Bcl-2 upregulation induced by miR-21 via a direct interaction is associated with apoptosis and chemoresistance in MIA PaCa-2 pancreatic cancer cells. Arch Med Res 2011;42:8-14.
31. Zhao C, Zhang J, Zhang S, et al. Diagnostic and biological significance of microRNA-192 in pancreatic ductal adenocarcinoma. Oncol Rep 2013;30:276-84.
32. Tang S, Bonaroti J, Unlu S, et al. Sweating the small stuff: microRNAs and genetic changes define pancreatic cancer. Pancreas 2013;42:740-59.
33. Liu Q, Chen J, Wang J, et al. Putative tumor suppressor gene SEL1L was downregulated by aberrantly upregulated hsa-mir-155 in human pancreatic ductal adenocarcinoma. Mol Carcinog 2014;53:711-21.
34. Biunno I, Appierto V, Cattaneo M, et al. Isolation of a pancreas-specific gene located on human chromosome 14q31: expression analysis in human pancreatic ductal carcinomas. Genomics 1997;46:284-6.
35. Cattaneo M, Orlandini S, Beghelli S, et al. SEL1L expression in pancreatic adenocarcinoma parallels SMAD4 expression and delays tumor growth in vitro and in vivo. Oncogene 2003;22:6359-68.
36. Huang C, Li H, Wu W, et al. Regulation of miR-155 affects pancreatic cancer cell invasiveness and migration by modulating the STAT3 signaling pathway through SOCS1. Oncol Rep 2013;30:1223-30.
37. Wang WS, Liu LX, Li GP, et al. Combined serum CA19-

9 and miR-27a-3p in peripheral blood mononuclear cells to diagnose pancreatic cancer. Cancer Prev Res (Phila) 2013;6:331-8.
38. Slater EP, Strauch K, Rospleszcz S, et al. MicroRNA-196a and -196b as Potential Biomarkers for the Early Detection of Familial Pancreatic Cancer. Transl Oncol 2014;7:464-71.
39. Zou X, Wei J, Huang Z, et al. Identification of a six-miRNA panel in serum benefiting pancreatic cancer diagnosis. Cancer Med 2019;8:2810-22.
40. Daoud AZ, Mulholland EJ, Cole G, et al. MicroRNAs in Pancreatic Cancer: biomarkers, prognostic, and therapeutic modulators. BMC Cancer 2019;19:1130.
41. Zhu S, Wu H, Wu F, et al. MicroRNA-21 targets tumor suppressor genes in invasion and metastasis. Cell Res 2008;18:350-9.
42. Zhao Y, Zhao L, Ischenko I, et al. Antisense inhibition of microRNA-21 and microRNA-221 in tumor-initiating stem-like cells modulates tumorigenesis, metastasis, and chemotherapy resistance in pancreatic cancer. Target Oncol 2015;10:535-48.
43. Sicard F, Gayral M, Lulka H, et al. Targeting miR-21 for the therapy of pancreatic cancer. Mol Ther 2013;21:986-94.
44. Nalls D, Tang SN, Rodova M, et al. Targeting epigenetic regulation of miR-34a for treatment of pancreatic cancer by inhibition of pancreatic cancer stem cells. PLoS One 2011;6:e24099.
45. Passadouro M, Faneca H. Combination of Anti-miRNAs Oligonucleotides with Low Amounts of Chemotherapeutic Agents for Pancreatic Cancer Therapy. Methods Mol Biol 2018;1699:135-54.
46. Passadouro M, Pedroso de Lima MC, Faneca H. MicroRNA modulation combined with sunitinib as a novel therapeutic strategy for pancreatic cancer. Int J Nanomedicine 2014;9:3203-17.
47. Negoi I, Hostiuc S, Sartelli M, et al. MicroRNA-21 as a prognostic biomarker in patients with pancreatic cancer - A systematic review and meta-analysis. Am J Surg 2017;214:515-24.
48. Namkung J, Kwon W, Choi Y, et al. Molecular subtypes of pancreatic cancer based on miRNA expression profiles have independent prognostic value. J Gastroenterol Hepatol 2016;31:1160-7.
49. Ohuchida K, Mizumoto K, Kayashima T, et al. MicroRNA expression as a predictive marker for gemcitabine response after surgical resection of pancreatic cancer. Ann Surg Oncol 2011;18:2381-7.
50. Yu J, Ohuchida K, Mizumoto K, et al. MicroRNA, hsa-miR-200c, is an independent prognostic factor in pancreatic cancer and its upregulation inhibits pancreatic cancer invasion but increases cell proliferation. Mol Cancer 2010;9:169.
51. Vrahatis AG, Dimitrakopoulos GN, Tsakalidis AK, et al. Identifying miRNA-mediated signaling subpathways by integrating paired miRNA/mRNA expression data with pathway topology. Annu Int Conf IEEE Eng Med Biol Soc 2015;2015:3997-4000.
52. Liu Y, Cui Y, Bai X, et al. MiRNA-Mediated Subpathway Identification and Network Module Analysis to Reveal Prognostic Markers in Human Pancreatic Cancer. Front Genet 2020;11:606940.
53. Zhang J, Gu J, Guo S, et al. Establishing and validating a pathway prognostic signature in pancreatic cancer based on miRNA and mRNA sets using GSVA. Aging (Albany NY) 2020;12:22840-58.
54. Wu X, Huang J, Yang Z, et al. MicroRNA-221-3p is related to survival and promotes tumour progression in pancreatic cancer: a comprehensive study on functions and clinicopathological value. Cancer Cell Int 2020;20:443.
55. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144:646-74.
56. Helms E, Onate MK, Sherman MH. Fibroblast Heterogeneity in the Pancreatic Tumor Microenvironment. Cancer Discov 2020;10:648-56.
57. Price C, Chen J. MicroRNAs in Cancer Biology and Therapy: Current Status and Perspectives. Genes Dis 2014;1:53-63.

Cite this article as: Fu RB, Chen X, Chen Y, Ye QH, Yang B, Shao Q, Zhu JH. Research progress on microRNAs as molecular markers in pancreatic cancer: a narrative review. J Gastrointest Oncol 2022;13(4):2048-2056. doi: 10.21037/jgo-22-577

