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The Impact of MiRNA on the Molecular Mechanisms of Invasion and Metastasis in Pancreatic Cancer

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Abstract: Pancreatic cancer is a highly malignant tumor with a poor prognosis. Due to its highly invasive and metastatic characteristics, its five-year survival rate is extremely low. miRNA is a class of non-coding single-stranded RNA molecules with a length of about 20-24 nucleotides encoded by endogenous genes. A large number of studies have shown that miRNA is involved in various regulatory modes such as post-transcriptional gene expression regulation in the process of pancreatic cancer development, metastasis and invasion. MiRNA dysregulation is often observed in cancer, leading to disease progression. More and more studies have revealed specific changes in miRNA expression patterns and how they lead to the development of pancreatic cancer. This article summarizes the current research progress of miRNA in pancreatic cancer invasion and metastasis, providing a theoretical basis and new targets for the early diagnosis and treatment of pancreatic cancer.

Keywords: MiRNA; Pancreatic Cancer; Invasion and Metastasis.

1. Introduction

Pancreatic cancer is a highly lethal malignant tumor. According to the latest data released by the American Cancer Society,[1]In 2024, it is estimated that there will be 66,440 new cases of pancreatic cancer and 51,750 deaths in the United States, making pancreatic cancer the third leading cause of cancer-related deaths in the country. In China, with changes in population structure, social environment, and increasing life stress, the incidence of pancreatic cancer has been steadily rising. The overall 5-year survival rate for patients is approximately 10%.[1–3]. There are many factors contributing to the high mortality rate of pancreatic cancer, with the primary factor being that the disease is often not detected until it reaches an advanced stage, typically after distant metastasis has occurred.[4]. Therefore, there is an urgent need to identify novel biomarkers that can aid in early detection and improve treatment strategies. miRNAs are small RNA molecules that play a crucial role in regulating gene expression by binding to messenger RNA (mRNA), thereby influencing protein production and downstream cellular functions. Over the past decade, miRNAs have become a significant focus of research in the field of pancreatic cancer. Abnormal miRNA expression has been associated with all major types of cancer, including pancreatic cancer.[5]. Dysregulation of miRNA expression leads to various hallmarks of cancer, such as uncontrolled cell proliferation, invasion, angiogenesis, metastasis, and evasion of tumor suppressor factors.[6–10]Therefore, exploring how miRNAs contribute to the invasion and metastasis of pancreatic cancer is of great significance for improving the survival rates of pancreatic cancer patients.

2. Overview of miRNA

MicroRNAs (miRNAs) are non-coding, post-transcriptional regulatory small RNA molecules. Numerous studies have shown that miRNAs are involved in various molecular signaling pathways and are closely related to the progression of several malignant tumors, including pancreatic cancer. miRNAs play a crucial role in a range of diseases, including cell growth, body development, viral infections, and tumor growth and invasion.[11–13]. Dysregulation of miRNAs is associated with most types of cancer and may be linked to various hallmarks of cancer.[14–16]This dysregulation may be caused by chromosomal abnormalities, epigenetic changes (such as CpG island hypermethylation), transcriptional regulation disturbances, or even direct interactions between two miRNAs, leading to the suppression of miRNA activity.[17,18]For example, miR-21 has been found to be more abundant in pancreatic tumors compared to non-tumor pancreatic tissue, and it can serve as a prognostic biomarker for pancreatic cancer.[19,20]A large number of studies have found that miRNAs can influence the invasion and metastasis of pancreatic cancer through multiple pathways, including extracellular matrix receptors (ECM), epithelial-to-mesenchymal transition (EMT), ferroptosis, autophagy, exosomes, co-action with long non-coding RNAs (lncRNAs), and regulation by N6-methyladenosine (m6A).

3. MiRNA Modulates Pancreatic Cancer Invasion and Metastasis by Involving ECM Processes

A key feature of pancreatic cancer is the extensive proliferation of connective tissue both within and around the tumor. This pro-fibrotic response often becomes a barrier to treatment and provides a pathway for cancer cell metastasis. [21] Therefore, efforts are being intensified to understand and target the stroma in pancreatic cancer, in combination with traditional, approved therapies, to improve treatment outcomes. A key player in the extracellular matrix (ECM) is the cancer-associated fibroblast (CAF), which is responsible for producing the majority of ECM components. As a result, CAFs and the matrix deposition and remodeling they mediate are often considered to promote tumor progression. In 2015, Pang and colleagues were the first to demonstrate that pancreatic cancer cells could promote the differentiation of normal fibroblasts into CAF/CAF-like cells by secreting extracellular vesicles containing miR-155. These

extracellular vesicles could directly interact with TP53INP1.[22]CAF has also been shown to interact with cancer cells through the secretion of miRNAs. In a recent study, co-culture of cancer cells with CAF-derived extracellular vesicles containing miR-331-3p promoted the in vitro proliferation, migration, and invasion of cancer cells, potentially by directly inhibiting scavenger receptor class A member 5 (SCARA5).[23]MicroRNAs have also been shown to play a role in regulating the secretion of matrix and matrix-modifying components. Studies have reported that differentially expressed miRNAs in pancreatic cancer patients are strongly associated with ECM organization and remodeling.[24]In this study, serum miRNAs were sequenced and found to be associated with key cancer-driving genes (such as KRAS) as well as other ECM-related genes (including matrix metalloproteinase 14 (MMP14), plasminogen activator urokinase (PLAU), and tenascin C (TNC)). Additionally, KRAS activation was found to be linked to the downregulation of miR-29 expression in pancreatic cancer, leading to increased CAF deposition of ECM proteins and promoting in vitro cancer cell colony formation.[25]Currently, there is limited understanding of miRNAs that specifically regulate the ECM in pancreatic cancer. Most miRNA sequencing studies of pancreatic cancer tumors have been performed on bulk tumor tissue samples, which overlook the heterogeneity of the tumor ecosystem. This makes it difficult to assign specific miRNA profiles to the ECM of pancreatic cancer. Future research is needed to better understand the specific roles of miRNAs in regulating ECM deposition, organization, and remodeling in pancreatic cancer.

4. MiRNA Modulates Pancreatic Cancer Invasion and Metastasis by Involving the EMT Process

Epithelial-to-mesenchymal transition (EMT) refers to the process by which epithelial cells gradually lose their inherent characteristics and functions, acquiring a mesenchymal cell phenotype. Studies have shown that EMT contributes to cancer cell metastasis.[26]EMT is a reversible biological process.[27]Cells with mesenchymal characteristics can also revert to an epithelial phenotype. The reverse process of EMT is called mesenchymal-to-epithelial transition (MET). These changes are closely related to tumor differentiation.[28]EMT is considered a prerequisite for cancer cell invasion and metastasis.[29]The development and progression of pancreatic cancer are accompanied by EMT characteristics, involving the precancerous evolution of pancreatic cancer cells, tumor progression, the tumor microenvironment, and EMT-related molecular networks. miRNAs can participate in the invasion and metastasis of pancreatic cancer cells by activating the PI3K pathway.[30]In the early stages of local invasion, miRNAs play a supportive role in migration by promoting EMT.[31,32]An example of a miRNA that promotes EMT is miR-361-3p, which directly targets dual specificity phosphatase 2 (DUSP2), activates the ERK signaling pathway, and facilitates EMT. This leads to increased invasion and migration of cancer cells in vitro. [33]The miR-200 family (miR-200a, miR-200b, miR-200c, miR-124, miR-429) is well known for its ability to maintain the epithelial state of cancer cells and prevent EMT. The expression of miR-200b and miR-200c is associated with the formation of tumor budding, a classic feature of EMT. Although the expression levels of the miR-200 family vary across different studies, they are generally upregulated in pancreatic ductal adenocarcinoma (PDAC) tumors compared to normal pancreas tissue.

Upregulation of miR-200 family members typically leads to the inhibition of the zinc finger E-box binding homeobox (ZEB) family, which is a key driver of EMT. This, in turn, relieves ZEB-mediated suppression of E-cadherin expression. E-cadherin is a critical adhesion molecule associated with the maintenance of the epithelial phenotype.[34–36]This effect has been confirmed in cells induced to undergo TGF-β-mediated EMT, where the expression of the miR-200 family is significantly reduced, accompanied by an increase in the expression of mesenchymal markers such as ZEB.[37]In pancreatic cancer, ZEB1 is a crucial contributor to EMT because it can seamlessly switch between transcriptional repressors and activators, depending on its interaction with co-activators such as Lef1, YAP1, P300, and Smad.[38,39]Several studies have revealed that multiple miRNAs, including let-7 and miR-183, are involved in the regulation of the Hippo pathway, which is a key factor in cancer development and metastasis. One example is LATS2, a direct target of miR-373. Downregulation of LATS2 promotes tumor growth, indicating that miRNAs have a significant impact on the Hippo pathway. [40–42]Let-7 also suppresses the progression of pancreatic cancer cells by upregulating the expression of Suppressor of Cytokine Signaling 3 (SOCS3), which in turn inhibits STAT3 phosphorylation.[43]miR-503 has been shown to bind to the 3' UTR of CCND1 mRNA, which encodes Cyclin D1, a key regulator of the cell cycle, and suppresses the proliferation of pancreatic cancer cells.[44]A recent study has shown that miR-24-3p can directly target ASF1B, which subsequently promotes an EMT phenotype in pancreatic cancer cells, leading to enhanced invasiveness in vitro.[45]

5. MiRNA and lncRNA Cooperation in Influencing Pancreatic Cancer Invasion and Metastasis

Long non-coding RNAs (lncRNAs) are a class of functional RNA molecules that can influence the fate of tumor cells.[46] LncRNAs typically consist of more than 200 nucleotides and can directly regulate cellular biological functions without being translated into proteins.[47] LncRNAs can act as competing endogenous RNAs (ceRNAs) to regulate miRNA expression. Changes in the affinity of ceRNAs for miRNAs or alterations in their own abundance can activate or hinder downstream signaling pathways, thereby promoting or inhibiting cancer transformation and malignant phenotypes. Studies have shown that overexpression of the lncRNA SNHG12 (small nucleolar RNA host gene 12) leads to a reduction in miR-320b, which promotes EMT, proliferation, and invasion in pancreatic cancer cells.[48]LncRNA PCED1B-AS1 can sponge miR-411-3p and, as a ceRNA, promote the upregulation of hypoxia-inducible factor 1-alpha (HIF-1α), thereby enhancing the proliferation and invasion of pancreatic cancer cells.[49]Studies have shown that lncRNA HCG11 competitively binds to miR-579-3p to enhance the expression of MDM2, thereby promoting pancreatic cancer cell growth, invasion, metastasis, and inhibiting apoptosis.[50] In addition to the aforementioned regulatory axes, many other lncRNA-mediated ceRNA networks influence the development and

progression of pancreatic cancer. For example, the THAP9-AS1/miR-484/YAP, MIR31HG/miR-193B, and MALAT1/miR-217/KRAS axes regulate tumor cell growth and survival.[51–53]In addition, AFAP1-AS1 targets and binds to miR-384, upregulating ACVR1 to induce the maintenance of pancreatic cancer stem cells.[54]The LINC00511/miR-29b-3p/VEGFA axis regulates angiogenesis in pancreatic cancer.[55]

6. MiRNAs Influence the Invasion and Metastasis of Pancreatic Cancer by Regulating Ferroptosis in Pancreatic Cancer Cells

Ferroptosis is a regulated form of cell death caused by the accumulation of lipid reactive oxygen species (ROS) resulting from iron overload. Ferroptosis plays a regulatory role in tumor metastasis, including the modulation of tumor cells, cancer stem cells, immune-related cells, and tumor angiogenesis. Given that miRNAs are involved in the ferroptosis process, ferroptosis-related miRNAs may also influence tumor metastasis.[56]LncRNA SNHG11 is highly expressed in pancreatic cancer patients and promotes VEGFA expression through miR-324-3p, thereby enhancing angiogenesis and promoting the invasion and metastasis of pancreatic cancer.[57]Studies have shown that miR-125a can regulate the ferroptosis process in pancreatic cancer cells by targeting Mfn2.[58]A study investigated the impact of normal fibroblasts (NF) and cancer-associated fibroblasts (CAFs) isolated from pancreatic tissue on gemcitabine (GEM) resistance in pancreatic ductal adenocarcinoma (PDAC). After GEM treatment, CAF-derived exosomes were identified as inhibitors of ferroptosis in PDAC cells. The CAF-derived exosomal miRNA, miR-3173-5p, led to decreased expression of ACSL4 in PDAC cells. This miRNA was found to be upregulated in pancreatic cancer tissues, with its levels further increasing after chemotherapy. Overexpression of miR-3173-5p in PDAC cells enhanced resistance to GEM and ferroptosis, while silencing miR-3173-5p produced the opposite effect. In a xenograft tumor mouse model, miR-3173-5p overexpression was associated with increased GEM resistance, downregulation of ACSL4, and enhanced Ki-67 expression within the tumor, indicating increased cell proliferation. These findings suggest that miR-3173-5p, delivered via CAF-derived exosomes, inhibits ferroptosis through ACSL4 downregulation and plays a role in GEM resistance in pancreatic ductal adenocarcinoma.[59]Several miRNAs have been found to influence the metastasis and invasion of pancreatic cancer by inhibiting ferroptosis. By further investigating the relationship between miRNAs and ferroptosis, we can gain valuable insights that may help in developing therapeutic strategies to target pancreatic cancer metastasis.

7. MiRNAs are Involved in the Regulation of Autophagy in Pancreatic Cancer Cells, Affecting the Invasion and Metastasis of Pancreatic Cancer

MiRNAs play a key role in coordinating the autophagy pathway. [60] The autophagy pathway coordinates a multi-stage homeostatic lysosomal degradation system that is widely utilized by cells under stress conditions, such as nutrient deprivation, hypoxia, and the presence of abnormal or misfolded proteins and defective organelles.[61]Various autophagy-related genes and proteins are regulated by miRNAs, often referred to as "autophagy-related miRNAs." Changes in the expression levels of autophagic vesicles can lead to dysregulation of the autophagy pathway, a phenomenon that may contribute to pathogenesis, including the development of cancer. Similarly, autophagy plays a dual role in carcinogenesis, acting both as a tumor suppressor and as a tumor promoter, depending on the context.[60,62,63]Analysis of the miRNA expression profile in pancreatic cancer may serve as a prognostic tool for predicting chemotherapy resistance and overall survival. Additionally, these miRNAs could be used as autophagy regulators, offering potential therapeutic avenues for managing pancreatic cancer.[64]MiRNAs play a crucial regulatory role in autophagy. Some miRNAs promote the autophagy pathway, leading to the destruction of pancreatic cancer cells, while others enhance anticancer effects by inhibiting autophagy.[65]For example, miR-7 and miR-372-mediated miRNA-associated autophagy inhibition can suppress the growth of pancreatic ductal adenocarcinoma (PDAC). The former induces the upregulation of mTOR, inhibiting autophagy induction and thereby suppressing tumor growth, proliferation, and metastasis. The latter is closely associated with ULK1 regulation, and its inhibition of autophagy significantly contributes to the suppression of cell proliferation.[66,67]It has been reported that changes in miR-506-3p in pancreatic ductal adenocarcinoma (PDAC) have various effects on cell apoptosis, autophagy pathways, and mitochondrial modifications, both in vitro and in vivo.[68]MiR-221 induces autophagy and apoptosis mechanisms, and promotes the limitation of pancreatic cancer cell proliferation. MiR-221 is closely associated with the inhibition of histone deacetylase 6 (HDAC6), a deacetylase involved in protein aggregate clearance and the autophagy pathway. Reduced miR-221 expression, through the overexpression of HDAC6, imparts oncogenic potential to pancreatic cells.[69]In addition, many cancers, including pancreatic ductal adenocarcinoma, express the NF-E1 transcription factor (also known as Ying-Yang 1, YY1). YY1 regulates tumor-promoting autophagy in cancer cells through the YY1/MiR-30a pathway.[70]

8. Exosomal miRNAs are Involved in Influencing the Invasion and Metastasis of Pancreatic Cancer

Exosomes are extracellular vesicles with a diameter of 30-150 nm, produced by various cells. They are surrounded by a lipid bilayer and contain a variety of biomolecules, including DNA, RNA, proteins, and lipids.[71]As mediators of cell communication, exosomes promote tumor cell proliferation and regulate apoptosis, angiogenesis, and immune suppression in local tissues upon reaching recipient cells.[72]As mediators of communication between tumor cells and distant cells, exosomal miRNAs can promote local invasion, EMT (epithelial-mesenchymal transition), and the establishment of pre-metastatic niches (PMNs) in distant organs in pancreatic ductal adenocarcinoma (PDAC) cells. Pancreatic cancer-derived exosomal miR-494 and miR-542-3p facilitate the formation of PMNs in pancreatic cancer by downregulating the expression of matrix metalloproteinases (MMPs) in the liver and promoting ECM (extracellular matrix)

deposition.[73]In the hypoxic microenvironment, exosomal miR-301a-3p is highly expressed and mediates M2 macrophage polarization by promoting the expression of the PTEN/PI3Kγ pathway. This, in turn, enhances pancreatic cancer cell invasion and EMT (epithelial-mesenchymal transition).[74]Given the molecular specificity of exosomes, exosomal miRNAs are emerging as a promising avenue for future pancreatic cancer liquid biopsy and therapy. Continued research into these molecules could provide valuable insights for the diagnosis and treatment of pancreatic cancer.

9. After being Regulated by M6A Methylation, miRNAs Influence the Invasion and Metastasis of Pancreatic Cancer

MiRNAs can be regulated by M6A methylation, thereby influencing the malignant progression of pancreatic cancer. To date, various chemical modifications have been identified, with m6A remaining the most abundant post-transcriptional modification found in messenger RNA (mRNA).[75]The m6A modification involves the methylation of the sixth nitrogen atom of adenine in RNA. Approximately one-third of mammalian mRNAs (with an average of 3-5 m6A sites per mRNA) have been shown to possess this modification.[76,77] m6A was first discovered in 1974.[78,79]The concept of reversible m6A modification was gradually introduced following the discovery of the first methyltransferase, Methyltransferase-like protein 3 (METTL3), in 1997.[80]METTL3 also promotes the invasion and migration of pancreatic cancer cells. The CSC/METTL3/miR-25-3p/PHLPP2/AKT/p70S6K signaling axis has been shown to accelerate the invasion and metastasis of pancreatic cancer.[82]METTL3 may play a role in regulating pancreatic cancer progression through the miR-380-3p/PTEN/Akt pathway.[83]METTL14 is highly expressed in pancreatic cancer and promotes the occurrence, proliferation, invasion and metastasis of pancreatic cancer through the miRNA-1-3p/Rap1B/cRAF/MEK/ERK pathway.[84]The adjuvant therapy of m6A methylation modification in pancreatic cancer still needs further research and verification to provide new ideas and methods for the treatment of pancreatic cancer.

10. Summary and Outlook

In this review, we demonstrated the differential regulation of miRNAs in the context of pancreatic cancer, and explored how miRNAs affect the invasion and metastasis of pancreatic cancer through multiple pathways such as participation in EMT, collaboration with lncRNA, regulation of tumor cell ferroptosis, autophagy, and exosomes. In the past few decades, the study of miRNAs has enabled people to better understand the molecular mechanisms of metastasis and invasion of pancreatic cancer, but the 5-year survival rate of pancreatic cancer has hardly improved. The main reasons are the late diagnosis of pancreatic cancer and resistance to treatment. Therefore, in the future, we can continue to study the biological significance of miRNAs in pancreatic cancer and explore the potential of miRNAs in early diagnosis and prognosis to improve the prognosis and survival of pancreatic cancer patients.

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