Review Article

Stem Cell INVESTIGATION

The role of exosomal microRNAs in pancreatic cancer

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Abstract: Pancreatic cancer is the third leading cause of cancer death in the United States. New therapeutic and diagnostic strategies are urgently needed to improve pancreatic cancer outcomes. Exosomes are endosome-derived extracellular vesicles containing cellular lipids, proteins, and microRNAs (miRNAs). Studies have shown that exosomal miRNAs are potential diagnostic biomarkers and therapeutic targets for various types of cancer. In this review, we summarize recent findings indicating the role of exosomal miRNAs in pancreatic cancer progression, therapeutic resistance, and biomarker development.

Keywords: Pancreatic cancer; exosome; microRNA (miRNA); biomarker; chemoresistance

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Pancreatic cancer

The pancreas is a gland organ of the digestive and endocrine system located in the left upper abdomen between the stomach and the spine. Pancreatic cancer broadly refers to tumors derived from tissues of the pancreas. Based on the tissues of origin, pancreatic cancer can be generally separated into endocrine tumors and exocrine tumors. Exocrine tissue-derived pancreatic ductal adenocarcinoma (PDAC) possesses the highest morbidity among all types of pancreatic cancer (1,2) and is the third leading cause of cancer death in the United States in 2019, as estimated by the National Cancer Institute (56,770 new cases; 45,750 death) (3). The 5-year survival rate of PDAC is 9.3% from 2009 to 2015 (4) contrasting to 67.1% for cancers in all sites during the same period (3). Based on the degree of progression, PDAC can be staged as localized cancer, cancer with regional invasion, or cancer with distal metastasis (4). Currently there are no biomarkers available for early detection of PDAC. The level of tumor marker carbohydrate antigen 19-9 (CA 19-9) is increased in the blood in 75–85% of PDAC patients, thus often serving as a biomarker for PDAC in clinical practice (5,6). However, circulating CA19-9 is not specific to PDAC, nor it is a good indicator of early stage PDAC (7). When PDAC is diagnosed at a localized stage, surgical resection, such as pancreaticoduodenectomy (Whipple's procedure), could be an option that offers a potential cure (8,9). However, the treatment of metastatic PDAC mainly stays on symptom control, such as pain management or palliative chemotherapy (10). Therefore, development of early detection biomarkers and new therapeutics for pancreatic cancer is urgently needed. Since the tumor microenvironment is critically involved in PDAC progression (11-13), and exosomes are mediators of intercellular communication in the tumor environment (14,15), recent effort has extended to explore the role of exosomes in the progression and potential management of pancreatic cancer.

Exosomes

Exosomes are a group of extracellular vesicles that function

in mediating intercellular communication via transferring biological materials (16). These extracellular vesicles are around 100 nm in diameter, with some variations noted by different reports (15,17,18). In the 1980s, detailed ultrastructural studies showed that vesicles are formed within multivesicular bodies (MVBs) and released to extracellular space when MVBs fused with the cell membrane during the differentiation process of immature red blood cells (19). These extracellular vesicles were coined as exosomes and were later found to be released from Epstein-Barr virus-transformed B lymphocytes and could trigger T-cell responses (20). Even later it was found that exosomes are derived from a variety of cell types, including prokaryotes and eukaryotes (15,16). It seems clear that exosomes are released from all types of cells examined thus far, and are detected in all biological fluids tested (17,18). The most commonly accepted surface markers for exosomes are tetraspanins, such as CD63, CD81 and CD9. In addition, Alix, Flotillin-1, Syntenin-1 and TSG101 are also established indicators of exosomes (16). The International Society for Extracellular Vesicles has recently stipulated the minimum requirement for exosome isolation and verification (21). In 2007, exosomes were reported to transfer genetic materials, such as mRNA and microRNAs (miRNAs) among different cell types (22), indicating a new regulatory pathway in intercellular communication. These observations, along with others, triggered a wave of research effort on cancer exosomal biology over the last decade (23-29).

The first report of PDAC exosomes was released in 2005, in which the human pancreatic cancer cell line Colo357 was used as a model to show that PDAC exosomes with heat shock protein 70 on the surface stimulate NK cells' migratory and cytolytic activity (30). Emerging evidences since then have demonstrated the involvement of exosomes in the pathogenesis, proliferation, metastasis, and chemoresistance of pancreatic cancer (30-32). For example, Kupffer cells in the liver were shown to specifically uptake pancreatic cancer exosomes, resulting in transforming growth factor β (TGFβ) secretion, which further stimulates fibronectin production by activating hepatic stellate cells to facilitate pancreatic cancer metastasis (33). Among all the components in the exosomal cargos, exosomal miRNAs have been most frequently reported to mediate the metastasis and drug resistance in human cancers, including pancreatic cancer (34-37).

Pancreatic cancer exosomal miRNAs

miRNAs are ~22 nucleotide long small, noncoding RNAs that negatively regulate target mRNA expression by binding to the 3' untranslated regions (38-41). It is estimated that about 70% of human mRNA transcripts are regulated by miRNAs, suggesting that miRNA regulation of gene expression is involved in almost all cellular processes, including carcinogenesis (41,42). Alterations of miRNA expression in human cancer, including pancreatic cancer, are well described (38,43-45). Pancreatic cancer cells display different miRNA profiles compared to normal pancreatic ductal cells, and circulating miRNAs have been explored to develop new biomarkers for pancreatic cancer (46-51). Expression of nearly 20 miRNAs was detected to be elevated in the circulation of pancreatic cancer patients, and the plasma miRNA signatures are potential biomarkers for detection of pancreatic cancer (52-59). These observations indicate the potential involvement of miRNAs in the pathogenesis and progression of pancreatic cancer. After miRNAs were found to be present in exosomes (22), exosomal miRNAs have been extensively profiled in various cancer model systems (60-65). Nevertheless, the first report about exosomal miRNAs in pancreatic cancer was published in 2013, describing the high expression of serum exosomal miR-17-5p and miR-21 in pancreatic cancer patients (66). Further studies have explored the involvement of exosomal miRNAs in pancreatic cancer progression and drug resistance, and the potential of exosomal miRNAs as biomarkers for pancreatic cancer.

Exosomal miRNAs as circulating biomarkers for pancreatic cancer

Even though many reports have shown the promise of circulating miRNAs as biomarkers for pancreatic cancer, there have been no miRNA-based detection available for clinical diagnosis or screening of the disease. One major challenge in the process of developing miRNAs as biomarkers for pancreatic cancer arises from the heterogeneous nature of the circulating miRNA populations. The miRNAs isolated from the circulation are presented in different forms, including protein bound or exosome associated miRNAs, and are derived from various cell types (15,67). This heterogeneity compromises the sensitivity and specificity of circulating miRNAs

for detection of pancreatic cancer. Selective isolation or detection of circulating miRNAs released from pancreatic cancer cells is a critical step in the development of miRNAs as biomarkers for this malignance. One potential strategy to achieve this is to analyze circulating exosomal miRNAs, which are likely enriched in cancer-derived miRNAs, since the transfer of exosomes from primary tumors to the circulation has been demonstrated in various model systems (68,69).

In this context, multiple exosomal miRNAs have been reported as potential biomarkers for pancreatic cancer. Higher expression of serum exosomal miR-17-5p and miR-21 was first observed in patients with pancreatic cancer as compared to patients with benign pancreatic diseases and healthy controls (66). Expression of a group of serum exosomal miRNAs, including miR-1246, miR-4644, miR-3976 and miR-4306, was found to be significantly upregulated in patients with pancreatic cancer when compared to patients with benign pancreatic disorders (70). An exosomal miRNA signature with high expression of miR-10b, miR-21, miR-30c, and miR-181a and low expression of miR-let7a is a better indicator of pancreatic cancer than the exosomal glypican-1 levels (71). The level of exosomal miR-191, miR-21, and miR-451a was significantly elevated in patients with pancreatic cancer and intraductal papillary mucinous neoplasm as compared to benign controls (72). Plasma exosomal miR-451a was shown by miRNA microarray to be a minimally invasive biomarker for the prediction of recurrence and prognosis of pancreatic cancer (73). Along with others, we have recently demonstrated that miR-196a and miR-1246 are highly enriched in pancreatic cancer exosomes, and that plasma exosomal miR-1246 and miR-196a levels are significantly elevated in patients with localized pancreatic cancer (63,64). In addition to the expression of miRNAs in plasma exosomes, the exosomal miRNAs in pancreatic juice were also examined in order to develop novel biomarkers for pancreatic cancer. In this study, exosomal miR-21 and miR-155 in pancreatic juice were shown as promising biomarkers for pancreatic cancer (74). Interestingly, miR-1246 and miR-4644 in salivary exosomes were also reported to be potential indicators of pancreatobiliary tract cancer (75). Furthermore, miR-4525, miR-451a, and miR-21 in portal vein blood were found to be potential biomarkers to evaluate the risk for recurrence and poor survival in patients with resected pancreatic cancer (76).

Overall, studies have shown the promise of exosomal miRNA signatures as biomarkers for detection and prognosis of pancreatic cancer. However, there has been no consensus as to which exosomal miRNA signatures are the best indicators of pancreatic cancer, and the results often vary among different studies, raising concerns of their reproducibility. Although this is likely in part due to different methods/models used for exosome isolation or various assays applied for miRNA analysis among the reports, the heterogeneous exosome populations (15) present in the circulation may contribute to the variability. Therefore, new strategies need to be explored to selectively analyze pancreatic cancer exosomal miRNA signatures in order to establish reproducible and clinically applicable circulating exosomal miRNA signatures for pancreatic cancer.

Exosomal miRNAs in pancreatic cancer progression

Intercellular communication via exosomal miRNAs is a significant signaling event in the tumor microenvironment (15,77-79). Studies have shown that exosomal miRNA signaling contributes to tumor progression in various cancer model systems (80,81). It has been reported that miRNAs contained in exosomes are transferred to recipient cells in the tumor microenvironment or distant organs where they can regulate target gene expression to promote tumor angiogenesis, immune responses, and metastasis (77,78,82). In the context of cancer exosomal miRNA profiles, studies have demonstrated that certain miRNA species are selectively enriched in cancer exosomes compared to exosomes released by normal epithelial cells, which may contribute to cancer progression (62,64,77,83). As for pancreatic cancer, a crosstalk among pancreatic stellate cells, cancer-associated fibroblasts, and pancreatic cancer cells was found to upregulate miR-21 and miR-221 expression, which may confer aggressiveness to pancreatic cancer (84). This crosstalk among different cell types is likely attributed to exosomal miRNA transfer. In a separate study, miR-23b-3p was found to be highly enriched in pancreatic cancer cell-derived exosomes, and overexpression of miR-23b-3p enhanced proliferation, migration, and invasion of pancreatic cancer cells (85). The differential expression of exosomal miR-339-5p was also found to be involved in the invasion and migration of pancreatic cancer cells (86). Interestingly, pancreatic cancer exosomes could increase invasion and proliferation of neighboring tumor cells through transferring miR-222 (87). Hypoxic tumor cell-originated exosomal miR-301a was found to mediate M2 macrophage polarization through PTEN/PI3K to assist pancreatic cancer metastasis

(37). On the other hand, M2 macrophage-released exosomal miR-501-3p suppressed tumor suppressor TGFBR3 gene expression, and helped promote pancreatic cancer development by activating the TGF-β signaling pathway (88). miR-126-3p derived from bone marrow mesenchymal stem cell (BMSC) exosomes was reported to suppress pancreatic cancer development via the downregulation of ADAM9 (89). Likewise, exosomal miRNA-1231 derived from BMSCs was found to suppress the activity of pancreatic cancer (90). Furthermore, exosomes derived from human umbilical cord mesenchymal stromal cells were reported to transfer exogenous miR-145-5p to suppress pancreatic cancer progression (91). Additionally, studies have shown that exosomal miRNAs may mediate immunosuppression in pancreatic cancer. For instance, exosomes derived from pancreatic cancer cells could be delivered to dendritic cells and suppress expression of the regulatory factor X-associated protein by transferring miR-212-3p, resulting in decreased MHC II expression (92,93).

While progress has been made in our understanding of the involvement of exosomal miRNAs in pancreatic cancer proliferation, invasion, and metastasis, questions remain as to how exosomal miRNAs are transferred from cancer cells to stromal cells and vice versa, and how they act to regulate target gene expression in recipient cells to promote pancreatic cancer progression. More studies are obviously required to better define the role of exosomal miRNAs in pancreatic cancer progression.

Exosomal miRNAs in chemoresistance of pancreatic cancer

Recent studies have shown that exosomal miRNAs are involved in mediating chemoresistance of pancreatic cancer. When treated with gemcitabine, a commonly used chemo drug for pancreatic cancer treatment, cancer-associated fibroblasts released more of the transcription factor Snail, as well as miR-146a, via exosome secretion. These exosomes were transported to surrounding pancreatic cancer cells and caused gemcitabine resistance of the recipient cells (94). Evidence showed that gemcitabine treatment of pancreatic cancer cells causes high expression of miR-155 in cancer cell-derived exosomes, which is transferred to neighboring cancer cells and causes gemcitabine resistance *in vitro* and *in vivo* (34). In line with this study, a recent report demonstrated that pancreatic cancer exosomes confer gemcitabine resistance in part via exosomal miR-155-mediated suppression of a key gemcitabine metabolizing gene (DCK) in recipient cancer cells. In this case, functional suppression of miR-155 or overexpression of DCK could lead to a decrease in exosomal miR-155-mediated chemoresistance (35). Another study showed that cancer-associated fibroblasts release exosomal miR-106b, which plays a significant role in inducing gemcitabine resistance of pancreatic cancer cells by targeting TP53INP1 (95). This finding suggests a new molecular target for sensitizing pancreatic cancer cells to gemcitabine. It has also been demonstrated that exosomes released by gemcitabine-resistant pancreatic cancer stem cells mediate the horizontal transfer of drug-resistant capabilities to gemcitabine-sensitive pancreatic cancer cells via transporting miR-210 (96), adding new information to our understanding of the exosomal miRNA-mediated gemcitabine resistance of pancreatic cancer. However our knowledge in exosomal miRNA-mediated chemoresistance is still quite limited, which encourages more studies on this specific research topic, given the clinical significance of overcoming chemoresistance for pancreatic cancer patients.

Conclusions

Pancreatic cancer is a deadly disease primarily attributed to diagnoses at late stages and the aggressive nature of the malignance. Better understanding of the biology of pancreatic cancer is critical for the development of new diagnostic and therapeutic strategies. Recent advancement in exosomal biology has demonstrated the involvement of exosomal miRNA signaling in pancreatic cancer proliferation, invasion, metastasis, and chemoresistance, thus revealing new potential therapeutic opportunities. Circulating exosomal miRNA signatures have been frequently described as potential non-invasive biomarkers for the detection and prognosis of pancreatic cancer. These promising research findings support further studies to explore strategies targeting exosomal miRNA signaling for pancreatic cancer therapy and establish exosomal miRNA signatures for early detection and monitoring of pancreatic cancer.

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Footnote

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