Chapter 1

Novel Implications of Exosomes and lncRNAs in the Diagnosis and Treatment of Pancreatic Cancer

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Abstract

Pancreatic cancer remains a leading cause of cancer-related deaths. Most patients are present with advanced stages of the disease at the time of diagnosis; thus, surgery, which is the best curative option for this malignancy, is no longer an effective treatment modality for affected individuals. As a likely source of "liquid biopsies," exosomes, which are secreted by fusing intracellular multivesicular bodies with cell membranes, have relative stability and composition, allowing them to cover the entire range of cancer-related biomarkers, including cellular proteins, lipids, DNA, RNA, miRNA, and long non-coding RNAs (lncRNAs). To explore the early detection biomarkers of pancreatic cancer and to develop successful therapeutic intervention for this disease, assessing the implications of exosomes in pancreatic cancer patients is essential. In this chapter, we wish to focus on the possibility of using exosomes and lncRNAs in the clinical management of patients with pancreatic cancer. We will discuss the mechanisms of tumor formation under the exosomal action, demonstrate how circulating exosomes and lncRNAs have come into the research spotlight as likely biomarkers of pancreatic cancer, and discuss the applications of exosomes as transfer vectors in tumor therapeutics.

Keywords: exosomes, lncRNA, pancreatic cancer, biomarkers, diagnosis, therapeutic intervention

1. Introduction

1.1. Exosomes, ncRNAs, and lncRNAs

Exosomes are a class of small (40–120 nm) extracellular vesicles (EVs) that originate in multivesicular endosomes [1–3] and can be released from a wide range of cells, including cancer cells [4]. Exosomes differ in size from microvesicles (50–1000 nm) and apoptotic bodies (800–5000 nm) and are secreted directly from the cell membrane in a budding form [5–7]. Late endosomes released from multivesicular bodies (MVBs) are integrated with the cell membrane in the extracellular matrix during the release of exosomes. Exosomes released into the extracellular environment can be utilized by tumor cells to alter the tumor microenvironment or to provide a favorable microenvironment for distant metastases by affecting distant organs [8–10]. Therefore, exosomes serve as efficient vehicles for long- and short-distance intercellular communication by signaling molecules in the form of lipids, proteins, DNA, RNAs, and non-coding RNAs (ncRNAs) [11]. Exosomes play an important role in signal transduction between cells.

In the complicated human genome, approximately 2% of the genomic sequence encodes proteins involved in biological progression [12], of which approximately 90% are ncRNAs. ncRNAs are described as the "noise" of the genome in their primary form, and they can be divided into two subgroups: small ncRNAs (sncRNAs) and long ncRNAs (lncRNAs) [13–16]. If RNA is <200 nt in length, the ncRNAs are defined as sncRNAs, which includes microRNAs (also called miRNAs or miRs). Conversely, long non-coding RNAs (lncRNAs) are >200 nt in length. Previous studies have reported that lncRNAs are involved in numerous physiological and pathological processes.

In recent years, an increasing number of lncRNAs have been investigated, and play a vital role in various major biological processes associated with promoting proliferation, invasion, and migration metabolism [17–19]. Increasing evidence points to important functional or regulatory roles of lncRNAs in cellular processes, including the cell cycle, proliferation, apoptosis [20–22], RNA processing [23], chromatin modification [24, 25], genomic reprogramming [26, 27], and gene imprinting [28]. They also play a role in cancers resulting from aberrant lncRNA expression. Recent findings indicate that lncRNAs are dysregulated in many kinds of cancer, including pancreatic cancer (PaCa), and they are closely related with tumorigenesis, metastasis, prognosis, and diagnosis.

2. The physiological function of exosomes

Exosomes carry a variety of substances from secreted cells, including proteins, lipids, DNA, RNA, and ncRNA [29, 30]. The intercellular communication regulated by exosomes is not only involved in regulating the physiological processes of normal cells but also participates in many pathological processes associated with disease development, including tumors [31–33]. Exosomes regulate biological activity through the rapid reaction of signal

molecules on their surface or by the release of extracellular biologically active substances. Exosomal biological activity is mainly determined by its components (i.e., the exosome cell source) [8–10]. Exosomes, which use autocrine, paracrine, and endocrine signaling to exchange biological information, are involved in the transmission of substances and signals between cells.

In addition, exosomes have immunomodulatory function [34]. Antigen-presenting cell (APC)-derived exosomes can promote the proliferation of T lymphocytes and induce anti-tumor immune responses in vivo. Exosomes have the features of their original cells because they bring DNA, RNA, and proteins from the original cell and carry a variety of proteins on their surface. Since exosomes are released from endosomes, they carry certain endosomal-specific proteins, including GTPases, flotillin, Alix, Tsg101, CD81 and CD82, heat shock proteins Hsp70 and Hsp90, and epithelial cell adhesion molecules [35–38] that are involved in exosome formation.

If exosomes are secreted by tumor cells, they can kill the tumor cells by providing information to cytotoxic T lymphocytes by cross-reacting with antigen-presenting cells [39]. However, exosomes from tumor cells have a dual role in that they have antitumor activity and also promote tumor growth. For example, exosomes from colorectal cancer cells contain cell cycle-related mRNAs that promote the proliferation of endothelial cells, which can induce tumor angiogenesis [40]. Exosomes obtained from gastric cancer cells promote tumor progression by activating the NF-kB pathway in macrophages [41]. In ovarian cancer, epithelial ovarian cancer (EOC) cell-derived exosomes promote ovarian cancer metastasis and deterioration by transferring CD44 to peritoneal cells [42].

3. Exosomes as novel biomarkers of cancer

The identification of cancer-specific exosomes in bodily fluids, such as serum, plasma, and urine, will be useful for the detection of cancer and will allow for the identification of specific DNA, RNA, and protein content in the absence of contamination from non-cancerous exosomes [43]. The proteoglycan glypican-1 (GPC1) is highly expressed in tumor cell-derived exosomes. GPC1 has been shown to be a specific, sensitive marker in serum from pancreatic patients that are in both the early and late stages but not in benign pancreatic diseases [43]. CD24 and EpCAM are tumor-derived exosome markers isolated by immune-affinity techniques involving anti-CD24 and anti-EpCAM magnetic beads [44]. In serum, CD24 and EpCAM serve as early diagnosis biomarkers [44], while fibronectin can serve as an early diagnosis biomarker in plasma. The ELISA method has been used to detect fibronectin [45]. The levels of exosomal EDIL3 from breast cancer patients can be dramatically reduced with surgery, indicating that EDIL3 can also serve as a diagnostic and prognostic biomarker [46]. Survivin expression has been shown to be significantly increased in patients with prostate cancer, but lower survivin expression has been found in benign prostatic hyperplasia (BPH) and healthy subjects. Additionally, the levels of survivin in BPH and healthy subjects are not significantly different. Thus, survivin can be used as a new diagnostic indicator of prostate cancer [47].

Separated and purified exosomes not only contain mRNA and miRNA but also tRNA and some lncRNA [11, 48–50]. Six miRNAs (miR-19b-3p, miR-21-5p, miR-221-3p, miR-409-3p, miR-425-5p, and miR-584-5p) were found to be upregulated in lung adenocarcinoma [51]. Eight miRNAs (miR-21, miR-141, miR-200a, miR-200c, miR-200b, miR-203, miR-205, and miR-214) have served as diagnostic biomarkers for ovarian cancer, and these miRNAs have also been identified in exosomes from ovarian cancer patients [52]. miRNAs can also be diagnostic biomarkers for esophageal squamous cell cancer (ESCC), as the serum levels of exosomal miR-21 from patients with ESCC are significantly higher than those of patients with benign diseases without systemic inflammation and are positively correlated with tumor progression and aggressiveness [53].

4. Exosomes for therapeutic intervention in cancer

The recent contribution by Zhang et al. reviewed the recent advances in cancer immunotherapy, exosome functions, exosome immunoregulation, and immune cell-derived exosomes [34]. As mentioned in Zhang's manuscript, exosomes cannot only transfer messages between cells by carrying RNA and proteins but also can modulate the immune response. After reviewing recent findings regarding exosomes and immunity in cancer, we have highlighted the novel insights into the development of efficient exosome-based cancer vaccines for cancer therapeutic intervention. Specifically, exosomes derived from immune cells, such as APCs, dendritic cells (DCs), and NK cells, play a crucial role in the immunomodulation of cancer, and they may be the best cancer vaccine candidates because they can inhibit the malignant activity of cancer cells and leave healthy cells unaffected [54–56]. Recently, researchers have noted that exosomes may lead to key advances in cancer therapy. Exosomes isolated from DCs have been evaluated in clinical trials as treatment for various kinds of cancers [57–59]. In a phase I clinical trial, exosomes derived from autologous DCs loaded with MAGE 3 peptides were applied as cancer therapy for stage III/IV melanoma patients [58]. Several phase I or phase II clinical trials involving exosome-based regimens have occurred in breast cancer, gastric cancer, malignant glioma, and non-small cell lung cancer patients, which demonstrates that exosomes are effective tools for the transportation of anticancer drugs [59]. Exosomes were employed to form a complex with curcumin and delivered to recipient pancreatic cancer cells, which was found to promote cytotoxicity [60]. Moreover, exosomes have been shown to deliver small, molecular anticancer drugs across the blood-brain barrier and significantly inhibit tumor growth in a brain cancer model [61, 62].

5. Long non-coding RNAs as novel biomarkers in cancer

lncRNAs modulate gene expression, while lncRNA dysregulation is associated with human cancer. lncRNAs could play a significant role in cancer progression by interacting with proteins. Since they are highly specific and easily detectable in tissue, serum, plasma, and urine, interest in exploring lncRNAs in cancer patients continues to increase. Metastasis-associated

lung adenocarcinoma transcript 1 (MALAT-1, also known as NEAT2), a novel lncRNA, is found on chromosome 11q13 and is well conserved among mammalian species. MALAT-1 is a critical regulator of the metastatic phenotype of lung cancer cells [63] and can enhance proliferation, cell motility, invasion, and metastasis in CNE-1 [64], lung adenocarcinoma [65], thyroid cancer [17], cervical cancer [19], and ovarian cancer cells [18]. MALAT-1 has an important role in regulating the metastasis of bladder cancer and can be a potential application in bladder cancer therapy [66]. The MALAT-1-mediated promotion of renal cell carcinoma (RCC) proliferation and metastasis may be due to the upregulation of Livin expression [67]. MALAT-1 promotes the proliferation of chondrosarcoma cells via activating the Notch-1 signaling pathway [68], indicates poor prognosis in non-small cell lung cancer, and induces migration and tumor growth [69]. Upregulation of MALAT-1 has been associated with survival rate, cell cycle, and migration in patients with esophageal squamous cell carcinoma (ESCC) [70]. However, the loss of MALAT1 is compatible with cell viability and normal development [71]. On the other hand, MALAT-1 is downregulated in preeclampsia and regulates the proliferation, apoptosis, migration, and invasion of JEG-3 trophoblast cells [72]. MALAT-1 is also expected to be a potential therapeutic target in prostate cancer [73]. As another critical oncogenic lncRNA in human cancers [74, 75], the lncRNA HOTTIP promotes tumor growth, inhibits cell apoptosis [76], contributes to the progression of prostate cancer [77] and non-small cell lung cancer [78] by regulating HOXA13, and increases the chemoresistance of osteosarcoma cells by activating the Wnt/β-catenin pathway [79]. HOTTIP is upregulated and associated with poor prognosis in patients with osteosarcoma [80]. Overexpression of HOTTIP can promote tumor invasion and predict poor prognosis in gastric cancer [81]. This accumulating evidence indicates that long non-coding RNAs have immense potential as powerful, non-invasive tumor markers. However, overexpression of HOTTIP inhibits glioma cell growth by brain and reproductive expression [82].

Circulating lncRNAs have shown potential as biomarkers in the diagnosis and prognosis of many cancers, including cervical cancer, colon cancer, hepatocellular carcinoma (HCC), gastric cancer (GC), PaCa, renal cell carcinoma (RCC), ovarian cancer (OC), non-small cell lung cancer (NSCLC), thyroid cancer, and prostate cancer (**Table 1**). Here, we have identified some interesting circulating lncRNAs (also known as exosomal lncRNAs), including MALAT-1, PVT1, HOTAIR, H19, UCA1, and TUG1, as novel biomarkers in various cancers. MALAT-1 in urine may serve as a potential biomarker for predicting prostate cancer risk. The application of the MALAT-1 model can prevent 30.2–46.5% of unnecessary biopsies in high-grade cancers [83]. PVT1 expression has been shown to be significantly elevated in non-small cell lung cancer (NSCLC), and high PVT1 expression has been associated with poor overall survival and disease-free survival in NSCLC patients; therefore, PVT1 could serve as a promising biomarker for the diagnosis and prognosis of NSCLC. PVT1 knockdown could remarkably inhibit NSCLC cell proliferation [84]. HOTAIR has been shown to be significantly higher in breast cancer patients, and circulating HOTAIR DNA levels were 2.15-fold higher in patients compared with those of healthy controls in one study, which demonstrates a moderate correlation between its expressions in tumor tissues. Plasma HOTAIR levels have been found to be significantly reduced after surgery [85, 86], indicating that plasma HOTAIR might serve as a potential biomarker for diagnosing breast cancer. A multivariate survival analysis also

lncRNA	Functions	Detection in cancer	References
MALAT-1	1. Promotes cell proliferation, invasion, and migration	Thyroid cancer, OC, cervical cancer, NSCLC, human nasopharyngeal carcinoma cell lines, bladder cancer, lung adenocarcinoma, JEG-3 trophoblast cells, PaCa, chondrosarcoma cell, RCC, ESCC	[17–19, 66, 67, 71–75, 77, 106]
	2. Regulator of the metastasis	Lung cancer cells, human nasopharyngeal carcinoma cell lines, PaCa	[65, 66, 111]
	3. Diagnostic and prognostic biomarker	Prostate cancer (urine/plasma), osteosarcoma (serum)	[78, 88, 123]
	4. Potential therapeutic target	Prostate cancer	[78]
HOTTIP	1. Inhibits glioma cell growth	Glioma	[87]
	2. Cell growth, apoptosis, migration, and invasion	HCC, PaCa, GC and colorectal cancer, NSCLC, lung cancer	[80, 81, 83, 85, 113, 123]
	3. Increases chemoresistance	Osteosarcoma cell, PaCa	[119]
	4. Progression and prognosis	Prostate cancer, colorectal cancer, osteosarcoma, tongue squamous cell carcinoma, PaCa, HCC	[80, 82, 119, 124–126]
	5. Biomarkers	PaCa (blood)	[121]
PVT1	1. Promotes cell proliferation and invasion	NSCLC, esophageal cancer, bladder cancer, acute promyelocytic leukemia, GC, BC	[127–133]
	2. Progression and prognosis	Cervical cancer, GC, HCC, PaCa	[115, 134–137]
	3. Promotes resistance	OC, GC	[138, 139]
	4. Modulates thyroid cancer cell proliferation	Thyroid cancer	[140]
	5. Apoptosis	Colorectal cancers	[141]
	6. Novel biomarker for diagnosis and prognosis	Cervical cancer, HCC, RCC (Serum); PaCa, NSCLC (tissue)	[89, 114, 142–145]
uc.345	1. Promotes tumorigenesis	PaCa	[122]
LINC-PINT	1. Diagnostic and prognostic biomarkers	PaCa (plasma and tumor tissues)	[127]

lncRNA	Functions	Detection in cancer	References
HOTAIR	1. Enhances cell proliferation, survival and migration	PaCa, HCC, cervical cancer, GC, OC, NSCLC, colorectal cancer, prostate cancer	[113, 146–155]
	2. Enhances its prognostic potential and correlates with disease progression	BC, HCC, cervical cancer, bladder cancer	[156–169]
	3. Relative to resistance	BC, cervical cancer, OC, bladder transitional cell carcinoma	[157, 160–162]
	4. Associated with EMT, cancer stem cells	Epithelial OC, colorectal cancer	[163, 164]
	5. Activates autophagy	HCC	[165]
	6. Modulates HLA-G expression	Cervical cancer, GC	[166, 167]
	7. Potential biomarker for diagnosis	PaCa, BC, colorectal carcinoma (serum/plasma), PaCa (tissue), GC (tissue, blood, and gastric juice)	[90, 91, 114, 149, 168–170]
H19	1. Promotes cell proliferation, migration and invasion	PDAC, lung cancer, BC, glioblastoma	[117, 172–174]
	2. Prognosis and progression and Metastasis	Gastrointestinal, colorectal cancer, NSCLC, gallbladder carcinoma	[175–179]
	3. Regulates angiogenesis	Glioma, glioblastoma	[173, 180]
	4. Contributing to resistance	OC	[181]
	5. Modulates tumorigenicity and stemness	Malignant carcinoma	[182]
	6. Regulatory role in pluripotency and tumorigenesis	Human embryonic carcinoma	[183]
	7. Promotes EMT	Colorectal cancer, esophageal cancer, glioblastoma	[173, 184, 185]
	8. Potential biomarkers for diagnosis	GC (serum/plasma/tissue), BC (tissue), bladder cancer	[91–93, 186–188]
IRAIN	1. Promotes proliferation and suppresses apoptosis	PaCa, NSCLC	[123, 189]
	2. As a novel imprinted gene that is aberrantly regulated in breast cancer	BC (tumors and peripheral blood leucocytes)	[190]

lncRNA	Functions	Detection in cancer	References
UCA1	1. Promotes the tumorigenesis, enhances cell proliferation, migration	PaCa, endometrial cancer, colorectal cancer, RCC, NSCLC, prostate cancer	[118, 191–194]
	2. Contributes to the progression and prognosis	OSCC, ESCC	[195, 196]
	3. Promotes EMT	BC	[197]
	4. Suppress metastasis	Epithelial OC	[198]
	5. Modulates cell growth and apoptosis, and epigenetic regulation	BC	[199, 200]
	6. Enhances drug resistance	BC, bladder cancer, GC, colorectal cancer, prostate cancer	[192, 201–205]
	7. Promotes glutamine metabolism	Bladder cancer	[206]
	8. As diagnostic and prognostic markers	HCC, colon cancer (serum), early gastric cancer, lung cancer (plasma), bladder cancer (urine and blood),	[171, 207–217]
TUG1	1. Promotes cell proliferation, migration	Bladder cancer, BC, osteosarcoma, ESCC, HCC	[218–222]
	2. Poor prognosis and promotes metastasis	Bladder cancer, GC, colorectal cancer, OC	[219, 223–226]
	3. Associated with chemotherapy resistance and poor prognosis	ESCC	[227]
	4. Acts as a tumor suppressor in human glioma	Human glioma	[228]
	5. Affects apoptosis and insulin secretion	PaCa	[124]
	6. As biomarker for poor prognosis	Osteosarcoma (plasma), B-cell neoplasms (plasma)	[229, 230]

Table 1. Long non-coding RNAs (lncRNAs) as potential biomarkers for cancer.

indicated that H19 might serve as a potential biomarker for early detection and prediction of prognosis of breast cancer and gastric cancer. The expression of H19 was remarkably increased in breast cancer and gastric cancer tissues. H19 expression has been shown to be significantly correlated with invasion depth, advanced TNM stage and regional lymph node metastasis in gastric cancer. Additionally, elevated expression levels of H19 have been shown to contribute to the poor overall survival and disease-free survival of gastric cancer patients [87]. This makes H19 closely associated with progressive gastric cancer, and it could be a potential non-invasive diagnostic gastric cancer biomarker for management. Better performance could be achieved

using both carcinoembryonic antigen (CEA) and H19 simultaneously [88]. Plasma H19 levels have been shown to be significantly decreased in postoperative breast cancer samples compared to those in preoperative samples [89]. Urothelial cancer-associated 1 (UCA1), originally identified as a lncRNA in bladder cancer, has been proven to play a pivotal role in bladder cancer progression and embryonic development. Upregulation of the lncRNA UCA1 and the lncRNA WRAP53 has been observed in hepatocellular carcinoma (HCC), and CA1 might serve as a novel serum biomarker for HCC. Moreover, the expression levels of UCA1 and WRAP53 in tissue have been shown to be strongly correlated with their levels in sera. Further, the combination of UCA1 and WRAP53 with serum alpha fetoprotein could improve sensitivity to 100% [90]. Further, meta-analysis also found that higher levels of UCA1 were correlated with shorter progression-free survival (PFS) and overall survival (OS) times in cancer [91], indicating that circulating lncRNAs, such as MALAT-1, PVT1, HOTAIR, H19, UCA1, and WRAP53, could serve as novel biomarkers for the early detection and the prediction of prognosis of cancer.

6. Exosomes and lncRNAs in the diagnosis and treatment of pancreatic cancer

Pancreatic cancer is one of the most lethal tumors, and its main tumor type is that of adenocarcinoma [92–94]. Pancreatic ductal adenocarcinoma (PDAC), the fourth leading cause of cancer-related deaths in both males and females in the USA, is usually asymptomatic [186], and PDAC is one of the most lethal malignant neoplasms worldwide [89, 95, 96]. Statistical analysis indicated that death rates rose from 2001 to 2010 [97]. In America, approximately 53,000 people were diagnosed with pancreatic cancer in 2016, and pancreatic cancer was responsible for 41,750 deaths in the USA [98] in that same year. Additionally, the incidence of pancreatic cancer has shown an increasing trend year-by-year in China, and pancreatic cancer has become one of the top 10 causes of cancer-related deaths [99].

It is well known that pancreatic cancer has a poor prognosis because it is usually diagnosed after the cancer has already spread, leading to poor patient outcomes. Pancreatic ductal adenocarcinoma patients have a 5-year survival rate of ~5% [100]. Survival can be improved if tumors are detected at an early stage, and the 5-year survival rate is 50% if tumors are <2 cm in size [101]. However, there have been no reliable biomarkers to accurately diagnose, image, or predict the tumor classification and biological behavior of pancreatic cancer until now. Thus, it is urgent to screen potential biomarkers and treatment-related biomarkers, such as exosome-derived proteins, DNA (exoDNA), miRNAs (exosomal miRNAs), and lncRNAs (exosomal lncRNAs), for the early detection of pancreatic cancer. Allenson found that KRAS mutations in the exoDNA of control, localized, locally advanced, and metastatic PDAC patients were 7.4, 66.7, 80, and 85%, respectively, which demonstrates that KRAS in exosomes could be applied to diagnose PDAC [102]. Takikawa also confirmed that pancreatic stellate cell (PSC)-derived exosomes stimulate the proliferation and migration of pancreatic cancer cells and upregulate the mRNA expression of the chemokine (C-X-C motif) ligands 1 and 2 in pancreatic cancer cells [103]. Over the last few years, non-coding RNAs, especially

exosomal lncRNAs and exosomal miRNAs, have become a new diagnostic, prognostic, and predictive tool for pancreatic cancer. Exosomal miR-155, miR-196a, miR-17-5p, miR-10b, and miR-21 have good sensitivity and specificity in the serum of PaCa patients and can be useful serum biomarkers for pancreatic cancer [104, 105]. Not only can single exosomes be a diagnosis biomarker, but combined exosomal miRNAs, such as miR-1246, miR-4644, miR-3976, and miR-4306, can also increase sensitivity and specificity for the diagnosis of pancreatic cancer.

Specifically, exosomal lncRNAs have been identified as potential biomarkers of various cancers in recent years, including gastric cancer, breast cancer, and lung cancer. However, few studies have explored the potential use of exosomal lncRNAs in pancreatic cancer detection and prognosis. MALAT-1, HOTTIP, PVT1, and HOTAIR, which are secreted from PDAC cells to bodily fluids, such as blood, pancreatic juice, cystic fluid, and urine, are some of most widely studied lncRNAs in pancreatic cancer (**Figure 1**). As a potential oncogenic lncRNA, MALAT-1 involves in proliferation, migration, and invasion and promotes the undifferentiated phenotype of pancreatic tumor cells [106]. MALAT-1 can also promote the tumorigenicity of pancreatic cancer cells, increase the proportion of pancreatic cancer stem cells, maintain a self-renewing capacity, and decrease chemosensitivity to anticancer drugs. Moreover, MALAT-1 has potential effects on the stem cell-like phenotypes of pancreatic cancer cells, which suggests that MALAT-1 has a novel role in tumor stemness [107]. The lncRNA HOTTIP enhances pancreatic cancer cell proliferation, survival, and migration and has been implicated in pancreatic cancer diagnosis and prognosis [108]. The overexpression of HOTAIR has been described as a poor prognostic factor in PDAC and can also be a novel non-invasive salivary biomarker for the early diagnosis of PaCa with PVT1 expression [109]. Increased expression of the lncRNA PVT1 is associated with poor prognosis in pancreatic cancer patients [110]. PVT1 expression is

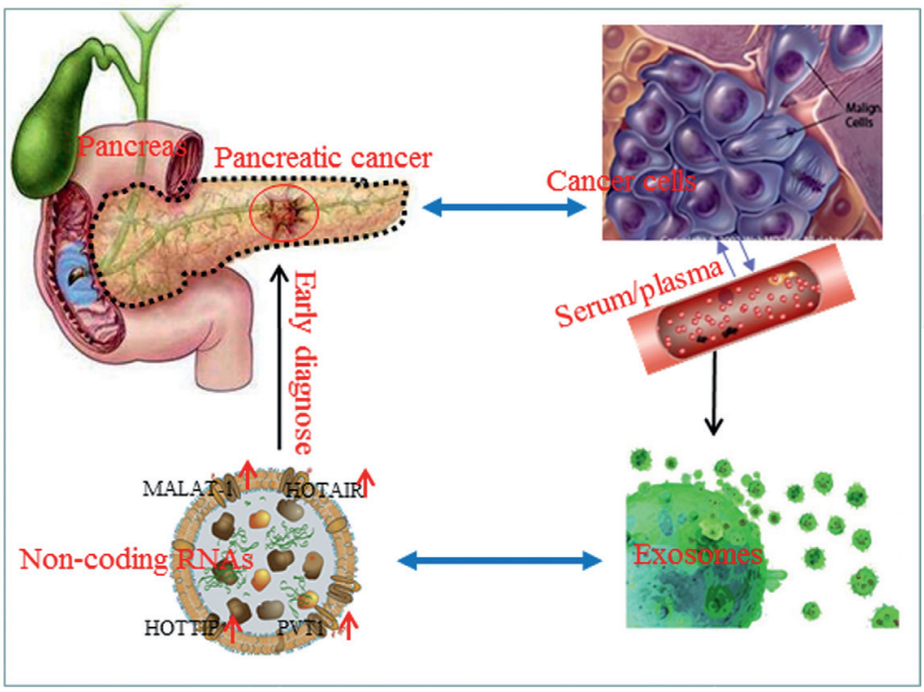

Figure 1. Exosomal lncRNAs secreted from PDAC cells as potential biomarkers of pancreatic cancer.

significantly increased in PDAC and is correlated with tumor progression. Moreover, patients with high PVT1 expression levels have been shown to have shorter overall survival times compared to those with low PVT1 expression levels, which implies that PVT1 could be a potential molecular biomarker for predicting the prognosis of patients with PDAC [110]. H19 has been shown to be overexpressed in PDAC tissues and to be correlated with the histological grade of PDAC. Knockdown of H19 can suppress cell viability, proliferation, and tumor growth, while H19 overexpression can enhance cell viability, proliferation, and tumor growth [111]. UCA1 expression has been shown to be significantly upregulated in PaCa tumor tissues and to be significantly correlated with malignant potential factors, such as tumor size, depth of invasion, CA19-9 levels, and tumor stage. Highly expressed UCA1 has been shown to be an independent prognostic biomarker of PaCa, leading to an obviously shorter 5-year overall survival (OS). Downregulation of UCA1 could effectively inhibit cell proliferative activities, which implies that UCA1 could be a potential prognostic biomarker and therapy target of PaCa [112].

In addition, high expression levels of the lncRNA HOXA13 have been shown to be correlated with lymph node metastasis, poor histological differentiation, and decreased overall survival in PDAC patients. The knockdown of HOXA13 resulted in proliferation arrest and impaired cell invasion in pancreatic cancer [113]. Using microarray analysis, HOTTIP was confirmed to be one of the most significantly upregulated lncRNAs in PDAC [113]. HOTTIP has been shown to be overexpressed in pancreatic cancer, and knockdown of HOTTIP in pancreatic cancer cells decreased proliferation, induced apoptosis, and decreased migration [108]. Using an Arraystar Human lncRNA Microarray, HOTTIP-005, XLOC_006390, and RP11-567G11.1 were found to be the most increased lncRNAs in PaCa. Elevated HOTTIP-005 and RP11-567G11.1 expression could serve as poor prognostic markers for patients with PaCa. Plasma HDRF and RDRF (HOTTIP-005- and RP11-567G11.1-derived RNA fragments in plasma/serum) have also shown to be significantly increased in patients with PaCa, which demonstrates that HDRF and RDRF levels could be promising indicators for distinguishing patients with PC [114]. As an oncogenic lncRNA, uc.345 has been shown to promote tumor progression and to serve as a poor predictor for OS in pancreatic cancer patients. uc.345 was found to be upregulated in tumor tissues, and higher uc.345 expression levels have been associated with cancer invasion and metastasis, which could be an independent risk factor for the OS of pancreatic cancer patients [115]. The lncRNA IRAIN plays an important role in many malignancies, and upregulation of IRAIN has been shown to be significantly correlated with tumor size, the TNM classification of malignant tumors (TNM) stage, and lymph node metastasis in PaCa patients. The knockdown of IRAIN significantly induced cell apoptosis and inhibited cell proliferation in PaCa cells [116]. The lncRNA TUG1 has been shown to be highly expressed in pancreatic tissue compared with its expression in other organ tissues, and downregulation of TUG1 has been shown to affect apoptosis and insulin secretion in pancreatic β cells [117]. CCDC26 might be identified as a novel oncogene in PaCa by regulating proliferating cell nuclear antigen (PCNA) and Bcl2 expression. CCDC26 is significantly upregulated in PaCa, and it is correlated with tumor size, tumor number, and reduced OS [118]. Univariate and multivariate analysis showed that CCDC26 expression can be an independent prognostic factor of OS in patients with PaCa; therefore, CCDC2 could serve as a novel biomarker and therapeutic target of PC for cancer in the future [118]. LINC-ROR has been shown to be upregulated in PaCa tissues, and overexpression of LINC-ROR promoted cell proliferation, migration, invasion,

and metastasis both in vitro and in mouse models. LINC-ROR acts as an important regulator of ZEB1 and might represent a novel therapeutic target [119]. The lncRNA LINC-PINT (p53-induced transcript) could also regulate tumor cell viability and proliferation. However, the expression levels of LINC-PINT have been shown to be lower in plasma and tumor tissue samples in PaCa patients. LINC-PINT has been shown to be more sensitive than CA19-9 in detecting PaCa, which suggests that LINC-PINT could be used for distinguishing the cause of malignant obstructive jaundice [120]. The lncRNA HMlincRNA717 has also been shown to be downregulated in pancreatic cancer and associated with overall survival, suggesting that HMlincRNA717 could be a potential prognostic biomarker for pancreatic cancer progression [121]. As a potential tumor suppressor, the long intergenic non-coding RNA (lincRNA) LINC00673 has been associated with pancreatic cancer risk. A G>A mutation at rs11655237 of LINC00673 created a target site for miR-1231 binding, which diminished the effect of LINC00673 in an allele-specific manner and conferred susceptibility to PaCa [122].

All the abovementioned exosomal lncRNAs could serve as diagnostic and prognostic factors to complement clinical and pathological parameters in predicting the outcome of patients with pancreatic cancer. Although there are an increasing number of clinical assays for studying exosomes, determining clinical applications for lncRNAs and exosomes is a long ways off. No matter how exosomes have become the most effective cancer vaccines, future research to investigate exosomal lncRNAs as biomarkers for the early detection of pancreatic cancer and to assess the validity and quality of the exosomes as effective vaccines for pancreatic cancer will be valuable. To achieve this long-term goal, further understanding of exosome biology, especially of the molecular mechanisms of tumor- and immune cell-derived exosomes as cancer vaccines, is required.

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Abbreviations

APC	Antigen-presenting cell
BC	Breast cancer
BPH	Benign prostatic hyperplasia
CEA	Carcinoembryonic antigen
DCs	Dendritic cells
EMT	Epithelial-mesenchymal transition
EOC	Epithelial ovarian cancer
ESCC	Esophageal squamous cell carcinoma
EVs	Extracellular vesicles
GC	Gastric cancer

HCC	Hepatocellular carcinoma
PCNA	Proliferating cell nuclear antigen
PFS	Progression-free survival
lncRNAs	Long non-coding RNAs
MALAT-1	Metastasis-associated lung adenocarcinoma transcript 1
ncRNAs	Non-coding RNAs
NSCLC	Non-small cell lung cancer
OC	Ovarian cancer
OS	Overall survival
OSCC	Oral squamous cell carcinoma
PaCa	Pancreatic cancer
PDAC	Pancreatic ductal adenocarcinoma
RCC	Renal cell carcinoma
sncRNAs	Small ncRNAs
UCA1	Urothelial cancer-associated 1

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