Exosome applications for the diagnosis and treatment of pancreatic ductal adenocarcinoma: An update (Review)

XINCHI LUAN[1*], XUEZHE WANG[1*], GANG BIAN[2], XIAOXUAN LI[3], ZIRU GAO[1], ZIJIAO LIU[4], ZHISHANG ZHANG[1], TIANYUE HAN[1], JINPENG ZHAO[1], HONGJIAO ZHAO[1], XINYUE LUAN[1], WUHUI ZHU[5], LILI DONG[2] and FEIFEI GUO[1]

[1]Pathophysiology Department, School of Basic Medicine, Qingdao University, Qingdao, Shandong 266071, P.R. China; [2]Department of Gastroenterology, Affiliated Qingdao Third People's Hospital, Qingdao University, Qingdao, Shandong 266041, P.R. China; [3]Department of Oncology, Key Laboratory of Cancer Molecular and Translational Research, The Affiliated Hospital of Qingdao University, Qingdao, Shandong 266031, P.R. China; [4]School of Clinical and Basic Medicine and Institute of Basic Medicine, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, Shandong 250117, P.R. China; [5]Department of Hepatobiliary Surgery, Affiliated Qingdao Third People's Hospital, Qingdao University, Qingdao, Shandong 266041, P.R. China

Received August 8, 2024; Accepted October 30, 2024

DOI: 10.3892/or.2024.8846

Abstract. Pancreatic ductal adenocarcinoma (PDAC) is a malignant neoplasm that typically manifests with subtle clinical manifestations in its early stages and frequently eludes diagnosis until the advanced phases of the disease. The limited therapeutic options available for PDAC significantly contribute to its high mortality rate, highlighting the urgent need for novel biomarkers capable of effectively identifying early clinical manifestations and facilitating precise diagnosis. The pivotal role of cellular exosomes in both the pathogenesis and therapeutic interventions for PDAC has been underscored. Furthermore, researchers have acknowledged the potential of exosomes as targeted drug carriers against regulatory cells in treating PDAC. The present article aims to provide a comprehensive review encompassing recent advancements in utilizing exosomes for elucidating mechanisms underlying disease development, patterns of metastasis, diagnostic techniques and treatment strategies associated with PDAC.

Correspondence to: Professor Feifei Guo, Pathophysiology Department, School of Basic Medicine, Qingdao University, 308 Ningxia Road, Qingdao, Shandong 266071, P.R. China
E-mail: gff72@163.com

Dr Lili Dong, Department of Gastroenterology, Affiliated Qingdao Third People's Hospital, Qingdao University, 29 Yongping Road, Qingdao, Shandong 266041, P.R. China
E-mail: wenxindll6688@126.com

*Contributed equally

Abbreviations: AUC, area under the curve; AUROC, area under the receiver operating characteristic curve; BRCA, breast cancer; CA19-9, carbohydrate antigen 19-9; CAAs, cancer-associated adipocytes; CAF, cancer-associated fibroblasts; CEA, carcinoembryonic antigen; cfDNA, cell-free DNA; circRNA, circular RNA; EVs, extracellular vesicles; GEM, Gemcitabine; GPC1, glypican-1; GSK-3β, glucose synthase kinase-3β; HCC, hepatocellular carcinoma; Hes-1, hairy and enhancer-of-split homolog-1; ILVs, luminal vesicles; KRAS, Kirsten rat sarcoma viral oncogene homologue; lncRNA, long non-coding RNA; MARCKS, myristoylated Alanine-Rich C-kinase Substrate; MHCs, major histocompatibility complex; MSCs, mesenchymal stromal cells; mFOLFIRINOX, modified FOLFIRINOX; MVBs, multivesicular bodies; PC, pancreatic cancer; PDAC, pancreatic ductal adenocarcinoma; PENVs, plant exosome-like nanovesicles; PTEN, phosphatase and tensin homolog; PTX, paclitaxel; ROBO1, roundabout guidance receptor 1; SEC, size exclusion chromatography; TAMs, tumor-associated macrophages; TME, tumor microenvironment; VEGF, vascular endothelial growth factor

Key words: PDAC, biomarker, exosome, treatment, diagnosis

Contents

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC), a highly invasive tumor that arises from the epithelial cells lining the pancreatic duct and constitutes ~80-90% of total pancreatic cancer (PC) cases (1,2). According to the GLOBOCAN 2022 data, there were a total of 510,566 newly diagnosed cases of PC worldwide in 2022, positioning it as the twelfth most prevalent malignancy

globally (3). Due to its insidious onset, diagnosing early stages of PDAC presents challenges. Most patients with this condition typically experience upper abdominal discomfort or exhibit initial symptoms such as dull pain and swelling.

Currently, the diagnosis of PDAC primarily relies on imaging examinations, complemented by the detection of serum biomarker carbohydrate antigen 19-9 (CA19-9) (4). The clinical diagnosis of PDAC often occurs at an advanced or even metastatic stage, primarily due to its low specificity and aggressive progression (5). The lack of efficacious targeted drugs further contributes to the suboptimal clinical diagnosis and prognosis of PDAC. Therefore, it is imperative to enhance early diagnostic and therapeutic approaches in order to improve the overall prognosis of PDAC (6). The activation of proto-oncogenes has been increasingly found to induce cancer cells to release a higher quantity of exosomes compared with healthy cells. This phenomenon significantly impacts the progression of PDAC through its transmission in both the tumor microenvironment (TME) and the entire body (7,8). Therefore, exosomes could be considered as promising diagnostic biomarkers for tumors, including PDAC (9-11).

Studies have explored the utility of exosomal markers such as B7-H4, Plectin-1, SATB2, Glypican-1 and microRNAs (miRNAs or miRs) in diagnosing PDAC and other related neoplasms (11-14). These exosomal markers have demonstrated potential in distinguishing between different types of PC, aiding in the accurate identification of malignant pancreatic intraductal papillary mucinous neoplasms and cholangiocarcinoma (15). Despite the challenges in validation, the use of exosomes as non-invasive diagnostic biomarkers is essential for the early detection of PDAC, a disease often diagnosed late due to its asymptomatic nature (16,17).

The ability of exosomes to transfer chemical agents has garnered significant interest across various fields. A study conducted by Zheng *et al* (18) demonstrated the protective effects of transplantation of mesenchymal stem cell-derived exosomes against Dox-induced cardiomyopathy. Chen *et al* (19) proposed that plant exosome-like nanovesicles (PENVs) and artificial PENV-derived nano-vectors hold immense potential for efficient delivery of therapeutic small RNA in mammalian systems, thereby showcasing promising prospects for future clinical applications. A previous study by Tamura *et al* (20) on the Myristoylated Alanine-Rich C-kinase Substrate (MARCKS)-ED-photodoxaz system presents a novel and promising approach for cancer treatment through targeted manipulation of exosomes and utilization of photochemistry. Kreger *et al* (21) reported that enrichment of Survivin in breast cancer (BRCA) cell-derived exosomes treated with Paclitaxel (PTX) promotes cellular survival and enhances resistance to chemotherapy. Additionally, engineered exosomes have been found to possess the ability to directly target cancer cells by transporting gemcitabine (GEM), PTX and other chemical agents (22). Overall, the literature suggests that exosomes possess the capability to transfer various molecules between cells, highlighting their potential in fields such as immunology, imaging and targeted therapy (23).

At present, there have been some reviews on the exosomes and PC (24-36). A review from Ariston Gabriel *et al* (31) in 2020 emphasizes the crucial significance of exosomes in both PC early diagnosis and treatment through involving in metastasis, cell proliferation, epithelial-mesenchymal transition (EMT), angiogenesis and TME of PC (31). In 2023, Fang *et al* (32) presented a comprehensive analysis elucidating the involvement of tumor-derived exosomes in various aspects of PC progression, including developing, progressing, diagnosing, monitoring and treating. Furthermore, the study of Bunduc *et al* (33) on utilizing exosomes for prognostic assessment in PDAC provides valuable perspectives. Expanding upon these findings, the classification of exosomes and their diverse mechanisms for diagnostic purposes are further reviewed, and the latest advancements in utilizing exosomes for the diagnosis and monitoring of PDAC are elaborated. Different from previous reviews that provide an overall summary of the role of exosomes in PC proliferation, invasion and metastasis, the present review lays out the roles of different types of bioactive molecules carried by exosomes including mRNA, miRNA, long non-coding RNA (lncRNA), circular RNA (circRNA), DNA and protein in early screening of PDAC. Additionally, the present review delves into the potential clinical applications of exosomes as efficacious drug delivery tools and the newly discovered bacterial exosomes are discussed. The current analysis further enhances this perspective by elucidating the early diagnosis and treatment potential of exosomes, thereby providing a comprehensive overview of recent advancements in utilizing exosomes for PDAC diagnosis and treatment.

2. Overview of exosomes

Extracellular vesicles (EVs) are a type of cell-secreted vesicles with a membrane structure, which can be categorized into three main groups based on their size, biological characteristics and formation process: Exosomes, microvesicles and apoptotic bodies (37,38). Exosomes typically refer to microvesicles with a diameter ranging from 30 to 150 nm that are formed through the fusion of multivesicular bodies (MVBs) with the cell membrane. In general, exosome biogenesis occurs through endosomal secretion in the early stages, facilitated by cytoplasmic membrane invagination within endocytic vesicles and subsequent multiplication during small body engulfment due to gradual lipid membrane fusion, resulting in the formation of early endosomes. During the process of endosome maturation, intracellular materials continue to be internalized by the cell membrane, leading to the formation of multiple luminal vesicles (ILVs), which eventually transform into MVBs. Finally, MVBs give rise to exosomes through their fusion with the plasma membrane and subsequent exocytosis of ILVs towards the extracellular space (39-41).

The secretion and release of exosomes is a precisely regulated process, with the involvement of various proteins such as Alix and TSG101 in exosome formation (42). Additionally, due to their role in signal transmission, the surface of exosomes typically contains four transmembrane proteins, including CD9, CD63 and CD81 (43). In addition to specific proteins, the phospholipid bilayer membrane of exosomes primarily comprises lipids and phospholipids, which are abundant in substances such as cholesterol, ceramide and sphingomyelin (44). The interaction between exosomes and cell surface receptors typically occurs through transmembrane proteins or lipid ligands, facilitating the delivery of exosomes and their internal proteins or nucleic acids to recipient cells

via endocytosis (45). Therefore, exosomes play a crucial role in intercellular communication and are indispensable for the development and progression of diseases (23,46). Moreover, exosomes are abundantly present in various body fluids (47,48). It has been confirmed that all cells have the ability to secrete exosomes (49). Cancer cells in patients with PDAC can transmit bioactive molecules through exosomes, thereby disrupting the gene expression signals of neighboring stroma or epithelium and other healthy cells. Compared with individuals without cancer, cancer cells in patients with PDAC have the ability to produce a significant quantity of diverse exosomes. Once identified, isolated and characterized using conventional methods, these exosomes can serve as potential biomarkers (50,51).

Recent advancements in exosome research have diversified the techniques available for isolation and purification, each with distinct advantages and limitations influencing their suitability for clinical applications. The conventional method for exosome purification is differential centrifugation, which has been considered the 'gold standard'. However, Lobb *et al* (52) demonstrated that a combination of ultrafiltration and size exclusion chromatography (SEC) can achieve comparable particle purity to density gradient purification and efficiently isolate a large quantity of exosomes from both cell culture media and human plasma. Tang *et al* (53) reported that ultracentrifugation exhibits the lowest yield and recovery but offers the highest protein purity compared with the other two exosome isolation methods (ExoQuick and Total Exosome Isolation Reagent). Vaswani *et al* (54) developed a robust protocol combining ultracentrifugation and SEC for isolating exosomes from human and bovine milk. Additionally, Tayebi *et al* (55) introduced an innovative approach in exosome research by integrating affinity-based methods with passive microfluidic particle trapping techniques. They utilized streptavidin-coated microbeads and biotinylated antibodies for targeted exosome capture, thereby enhancing isolation specificity. This method significantly reduces background noise during fluorescence-based quantification, though its dependency on specific antigen-antibody interactions may limit broader applicability. The diversity of these methodologies illustrates the ongoing evolution of exosome isolation and purification techniques, each contributing uniquely to the field's understanding and potential clinical applications.

TME plays a pivotal role in the progression of cancer and the failure of therapy (56). Tumor-associated macrophages (TAMs) are recruited to the TME and have been demonstrated to exert influence on cancer progression (57). Exosomes, nano-sized bio-vesicles released into bodily fluids, have been implicated in shaping the TME and contributing to cancer advancement (58). Macrophage-derived exosomal miR-501-3p has been shown to promote PDAC progression (59). A previous study has demonstrated the presence of glypican-1 (GPC1) positive exosomes in the serum of patients diagnosed with PDAC, exhibiting remarkable specificity and sensitivity. Moreover, these exosomes have shown potential in distinguishing individuals with benign pancreatic diseases or healthy subjects from those afflicted by both early and late-stage PDAC (22). Furthermore, TAMs are resident innate immune cells within the TME that actively contribute to tumor development and progression (60). The metabolic regulation governing heterogeneity among TAMs and their modulation by the TME remain areas necessitating further investigation (61). Overall, exosomes derived from macrophages play a significant role in shaping PDAC advancement as well as influencing dynamics within the TME itself (57,59). Extensive prior research has demonstrated that macrophages and fibroblasts within the TME participate in various stages of tumor development through diverse pathways (62). By engaging in bidirectional signaling with tumor cells and other cells via cancer-associated fibroblast (CAF)-derived cytokines, chemokines, growth factors and exosomes within the TME, CAFs not only promote tumor proliferation but also induce immune evasion of cancer cells. Exosomes derived from macrophages play a crucial role in the progression of PDAC and contribute to the dynamics of the TME by promoting M2 macrophage polarization. Exosomes originating from lung tumor cells, hepatocellular carcinoma (HCC) cells and *Schistosoma japonicum* adult worms have demonstrated their ability to modulate transcriptional and bioenergetic profiles of macrophages, inducing their polarization towards an M2 phenotype (63,64). These findings provide compelling evidence for a novel function played by exosomes in driving M2 macrophage polarization, thereby offering promising therapeutic targets for immunotherapy against lung cancer, HCC and PDAC (65,66). These findings underscore both the potential of targeting exosomes and TAMs for cancer therapy as well as emphasize the importance of comprehending their roles in driving cancer progression (67,68).

Furthermore, exosomes have the ability to transport and deliver diverse biological substances (69,70), thereby specifically targeting cancer cells or genes implicated in PDAC development. Consequently, engineered exosomes carrying specific targeted genes can be harnessed for the treatment of PDAC, thus playing a pivotal role in its therapeutic approach (71).

Exosomes have emerged as a promising non-viral delivery system for CRISPR/Cas9 gene editing in PDAC. McAndrews *et al* (72) demonstrated the ability of exosomes to encapsulate CRISPR/Cas9 plasmid DNA and efficiently deliver it to recipient cancer cells, thereby inducing targeted gene deletion. This approach has been shown to effectively suppress proliferation and inhibit tumor growth in preclinical models of PDAC. The objective of Su *et al* (73) was to elucidate the mechanisms underlying exosome-mediated intercellular communication between PC (Panc-1) cells and macrophages (J771.A1) using a Transwell co-culture system. Based on these findings, targeted genetic therapies aimed at selectively manipulating the content of tumor cell-derived exosomes, exhibiting significant potential for cancer therapy.

Exosomal heat shock protein 60 plays a pivotal role in intercellular communication, particularly in the progression of cancer (74). It holds potential clinical applications as a biomarker for diagnostics, prognostic assessment, and monitoring disease progression and treatment response in cancer. Moreover, heat shock protein 70 is upregulated in PDAC cells and inhibits caspase-dependent apoptosis, thereby facilitating cell survival (75). Heat Shock Factor 1, a protein that governs the heat shock response pathway, represents a promising target for drug intervention in cancer and proteinopathy with significant implications for therapeutic strategies and prognoses (76).

In a study conducted by Jin *et al* (77), it was discovered that exosomal ZIP4 promotes the growth of PDAC and serves as a novel diagnostic biomarker for this disease. Another study by Castillo *et al* (78) involved a comprehensive profiling of the 'surfaceome' of PDAC exosomes to identify surface proteins that could facilitate the enrichment of cancer-derived exosomes in liquid biopsies for subsequent molecular profiling. These studies suggest that utilizing small molecule inhibitors delivered via exosomes may offer potential therapeutic and diagnostic options for PDAC.

Exosomal nanoparticles secreted by human pancreatic tumor cell lines exert an inhibitory effect on tumor cell proliferation through the mitochondria-dependent apoptotic pathway, mediated by the activation of phosphatase and tensin homolog deleted on chromosome 10 (PTEN) and glycogen synthase kinase-3β (GSK-3β) (79). The interaction between exosomal nanoparticles and cells is considered to involve membrane lipid rafts. This interaction leads to a downregulation in the expression of hairy and enhancer-of-split homolog-1 (Hes-1), a key intranuclear target of the Notch-1 signaling pathway, as well as induction of apoptosis following G0/G1 phase cell cycle arrest (80,81). Unexpectedly, blocking presenilin results in PTEN and GSK-3β activation. Conversely, inhibition of either PTEN or GSK-3β increases Hes-1 expression and partially counteracts the proliferation inhibition induced by exosomal nanoparticles, highlighting reciprocal regulations between Notch signaling and PTEN/GSK-3β (82).

The present review focuses on the latest advancements concerning exosomes in early screening and treatment of PDAC. The aforementioned exosomes-related content was summarized to explain the roles of exosomes (Fig. 1).

3. Dual function of exosomes in PDAC

A wide range of studies have consistently demonstrated that exosomes participate in cellular processes such as cell migration, invasion, immune regulation, angiogenesis and cancer cell metastasis (83-85). During PDAC progression, malignant tumor cells release exosomes that exhibit a dual function. They not only facilitate cancer growth but also stimulate fibroblasts within the TME, resulting in alterations in immune cell subtypes among host cells (86,87). Consequently, this process hampers effective targeting of immunocytes towards cancer cells while simultaneously upregulating immunocyte apoptosis' levels.

On the one hand, exosomes that promote the progression of PDAC may serve as specific diagnostic markers and therapeutic targets. Jin *et al* (77) discovered that exosomes derived from PC-1.0 (a highly malignant pancreatic cell line) cells can be internalized by and enhance the proliferation, migration and invasion abilities of PC-1 (a moderately malignant PC line) cells. Wang *et al* (88) found that hypoxic exosomes derived from PC cells activate macrophages to adopt the M2 phenotype in a HIF1α or HIF2α-dependent manner, thereby facilitating the migration, invasion and EMT of PC cells. Chiba *et al* (89) demonstrated through *in vitro* analyses that exosomes released from PC (PK-45H) cells induce various gene expressions in human umbilical vein endothelial cells (89). These findings suggest that exosomes released from PC cells may serve as novel promoters of angiogenesis. Furthermore, exosomes play a crucial role in the TME and mediate communication between PDAC cells and matrix components such as pancreatic stellate cells, regulating the progression of PDAC (90). Zhou *et al* (91) confirmed that exosomes derived from PDAC cells can stimulate lymphangiogenesis both *in vitro* and *in vivo*. This mechanism is related to downregulation of ABHD11 antisense RNA 1 expression in lymphatic endothelial cells and enhancement of their proliferative capacity, migratory potential and tube formation ability (91).

On the other hand, exosomes that inhibit the progression of PDAC could also be utilized as carriers for drug delivery. For instance, exosomal miR-485-3p derived from pancreatic ductal epithelial cells suppresses PDAC metastasis by targeting p21-activated kinase-1 (92). The miR let-7b-5p is highly enriched in exosomes derived from NK cells and actively contributes to their antitumor effects against PDAC cells (93). In addition, exosomal miR-3607-3p derived from natural killer cells inhibits the progression of PDAC by targeting IL-26 (94). The downregulation of lncRNA SBF2-AS1 in M2 macrophage-derived exosomes leads to an increase in miR-122-5p, which restricts X-linked inhibitor of apoptosis protein and limits the development of PDAC (95). The suppression of pancreatic ductal cell carcinoma is achieved by human umbilical cord mesenchymal stem cell-derived exosomes carrying hsa-miRNA-128-3p, which exert their inhibitory effects on Galectin-3 (96). The specific mechanism underlying the dual nature of exosomes remains to be elucidated, potentially attributed to their diverse origins.

4. Utilizing exosomes for screening PDAC

The early stage of PDAC, characterized by a high degree of malignancy, often presents without evident clinical manifestations. As the disease progresses, patients commonly experience symptoms such as unexplained weight loss, tenderness in the upper abdomen and jaundice. Consequently, clinicians typically rely on these symptomatic presentations for diagnosing PDAC (97,98).

In clinical practice, following the assessment of genetic history and conducting a physical examination, clinicians commonly utilize blood tumor markers for the diagnosis of PDAC. Prominent diagnostic markers include CA19-9, carcinoembryonic antigen (CEA) and CA125. Among these, CA19-9 exhibits a specificity ranging from 80-90% in patients with PDAC and is considered the most sensitive tumor marker for diagnosing PDAC (99,100). However, based on scientific research, it has been observed that the CA19-9 biomarker may produce false positive outcomes in conditions such as cholangitis, inflammation and biliary tract obstruction, thereby compromising its accuracy in indicating the presence of a tumor (101). Moreover, ~15-25% of patients with early-stage PDAC exhibit CA19-9 levels below the clinical threshold of 37 U/ml (102), while Lewis antigen-negative individuals within the general population (5-10%) do not produce CA19-9 at all (102). Furthermore, achieving early detection and prompt treatment through these aforementioned methods remains challenging due to the relatively concealed pathogenesis of most cases (103). According to research findings, a significant proportion of patients receive their diagnosis when the disease has already progressed to either the intermediate or

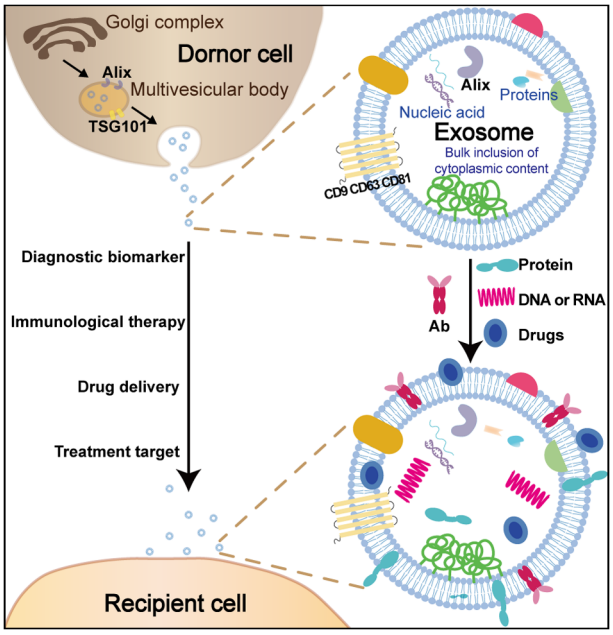

Figure 1. Application of exosomes in the treatment of pancreatic cancer. Exosomes can be utilized for the delivery of anticancer drugs, such as chemotherapy drugs and functional RNA, including small interfering RNA and microRNA. Additionally, peptides can be delivered to target cancer cells. Tumor-specific markers secreted by cancer cells outside the exosomes can be employed as a target, and the exosomes contain antibodies against the protein.

advanced stages. Consequently, there is a risk of overlooking potential opportunities for administering optimal treatment by relying solely on conventional diagnostic methods (104). Therefore, in accordance with the recommendations outlined in the latest literature, comprehensive diagnosis of PDAC includes utilization of the CA19-9 marker alongside histopathology, imaging techniques and other biomarkers (105,106). Recent studies have indicated that PDAC occurrence involves multitude cytokines, including miRNA, mRNA, DNA and exosomes (107,108). Given their detectability during PDAC development, exosomes hold great potential as diagnostic biomarkers for this disease (109).

The levels of exosomes were quantified in patients with PDAC, and the results revealed a statistically significant elevation compared with that observed in healthy controls. Additionally, there was a positive correlation between exosome levels and elevated serum CEA concentrations. Further analysis revealed a significant association between higher exosome levels, lower tumor differentiation and shorter overall survival (110). Exosome levels in PDAC vary across different stages and are correlated with disease severity (111). Significant variations in exosomal miR-10b levels among different stages of PDAC have been previously demonstrated (112). Furthermore, exosome-mediated communication contributes to the development of liver metastases in PDAC. However, comprehensive demonstration and validation are still required to establish the diagnostic validity and accuracy of exosomes for PDAC (113).

Simultaneously, bioactive molecules carried by PDAC promote cell migration and invasion (45,114); upon absorption by cancer cells, the physiological state of these cells undergoes changes leading to metastasis and spread to other parts of the body (115). Therefore, different types of bioactive molecules carried by exosomes including mRNA, miRNA, lncRNA, circRNA, DNA and protein can partially reflect the extent of tumor lesions in patients with PDAC; thus they can serve as biomarkers for early liquid biopsy screening for PDAC (33,116-118).

Exosomal non-coding RNA related to PDAC

MiRNAs. The application of serum exosome diagnosis has been suggested by numerous studies for early detection of PDAC (57,88,119). Among them, miRNA, a key regulator of post-transcriptional gene expression, is one of the most prevalent RNA species encapsulated within exosomes. Marin *et al* (120) highlighted that the levels of miR-125b-3p, miR-122-5p and miR-205-5p in serum exosomes from patients with PDAC were significantly elevated compared with those in the control group. Wang *et al* (121) conducted a study where they collected blood samples from patients with PDAC, chronic pancreatitis, and a healthy control group. Interestingly, it was identified that the level of miR-19b in patients with PDAC was significantly higher compared with both patients with chronic pancreatitis and the control group. Furthermore, when compared with the detection of the biomarker CA19-9, miR-19b exhibited superior diagnostic accuracy [area under the curve (AUC): 0.942 vs. 0.813, P=0.0054] (121).

In addition to their direct application in biomarker diagnosis, the integration of exosomes with existing indicators in clinical diagnosis and treatment of PDAC may significantly enhance the precision of medical interventions. Nakamura *et al* (122) demonstrated that by combining miR-21 and miR-155 analysis from pancreatic juice with pancreatic juice cytology, the diagnostic accuracy increased from 83, 89 and 74% for individual markers to a combined accuracy of 91% (122). The combination of miR-21, miR-210 and CA19-9 by Wu *et al* (110) was also found to enhance the diagnostic accuracy from 83-85 to 90%. However, the rapid progression of PDAC necessitates invasive surgical procedures combined with biomarkers for disease staging, thereby impeding timely and effective assessment of patient progress (110).

The study conducted by Chen *et al* (123) involved the classification of patients with PDAC based on disease progression and lymph node metastasis. Their findings revealed a significant decrease in the expression level of miR-1231 in the serum of patients, which was directly associated with disease advancement. Notably, stage I/II patients exhibited significantly lower levels of miR-1231 compared with stage III/IV patients, and this reduction correlated negatively with tumor metastasis extent. These results suggest that miR-1231 can serve as a valuable tool for evaluating PDAC progression (123). Another study consistently demonstrated a significant correlation between exosomal miRNA levels and tumor metastasis extent (124). This investigation focused on miR-451a as a research target and revealed its substantial association with clinical stage and distant metastasis. Moreover, the expression level of miR-451a was highly responsive to treatment and recurrence, suggesting its potential utility as an efficacy evaluation tool. In another multicenter cohort study by Nakamura *et al* (102), 15 out of 30 overexpressed miRNAs in exosomes or cytosol were identified through transcriptional analysis as suitable for establishing

a risk prediction model for diagnosing patients with PDAC using logistic regression analysis. The results simultaneously confirmed that the predictive model exhibited significantly higher accuracy in correctly identifying patients with either positive or negative CA19-9 compared with biomarker detection, particularly in distinguishing patients with stage I/II PDAC.

lncRNAs. lncRNA is a type of non-coding RNA that plays a crucial role in maintaining the stable biological function of PDAC cells through its interactions with miRNA, mRNA, DNA, or protein molecules. Yu *et al* (125) conducted an analysis on the differential expression of lncRNAs between patients with PDAC and healthy individuals and observed a significantly elevated level of exosome LINC00623 in patients with PDAC compared with healthy individuals. Specifically, the expression level of exosome LINC00623 in patients with PDAC was found to be ~3.7-fold higher than in healthy controls, with a 95% confidence interval of 2.8 to 4.5 fold increase (P<0.01) (125). *In vitro* experiments also demonstrated that exosome LINC00623 can bind to N-acetyltransferase 10 and maintain the stability of oncogenic mRNA through ac4C acetylation, indicating that lncRNA may serve as a potential biomarker for PDAC analysis.

Circ-RNAs. The presence of circRNA, along with miRNAs and lncRNAs, has also been detected in small EVs known as exosomes. Both circRNA and exosomes have recently demonstrated significant roles in various types of tumors. For instance, circ-KIAA1244 released in plasma exosomes has been identified as a potential marker for gastric cancer detection, with a sensitivity of 77.42% and a specificity of 68.00%. Similarly, hsa_circ_0004771 has been used to distinguish colorectal cancer, with an AUC of 0.88 (95% CI, 0.815-0.940), a sensitivity of 80.91%, and a specificity of 82.86%. Additionally, circ_0070396 combined with alpha-fetoprotein demonstrated 81.98% sensitivity and 100% specificity in the diagnosis of hepatocellular carcinoma (126).

The study conducted by Li *et al* (90) revealed a significant association between elevated circ-PDE8A expression and lymphatic invasion, Tumor-Node-Metastasis stage, as well as an unfavorable prognosis in patients with PDAC. Hong *et al* (126) demonstrated a significant correlation between the expression levels of exosome circRNA hsa_circ_0006220 and hsa_circ_0001666 with CA19-9 *in vivo*. Additionally, hsa_circ_0006220 was found to be involved in tumor metastasis, while hsa_circ_0001666 showed a significant association with tumor size (126).

By investigating the presence and expression levels of serum exosomal circRNAs, it may be possible to distinguish patients with cancer from healthy individuals in the future, thereby identifying novel potential exosome-based cancer biomarkers.

Exosomal DNA and proteins related to PDAC

DNA. Exosomes originate from viable cancer cells and may reflect a distinct biology compared with circulating cell-free DNA (cfDNA) released from dying tissues. Yadav *et al* (127) provided an in-depth analysis of the current status of liquid biopsy in PDAC as both diagnostic and therapeutic tools, while also discussing future research perspectives focusing on circulating tumor cells, circulating tumor DNA and exosomes. The study conducted by Allenson *et al* (128) compares exosome-derived DNA with cfDNA in liquid biopsies of patients diagnosed with PDAC, revealing a high prevalence of mutant Kirsten rat sarcoma viral oncogene homologue (KRAS) in circulating exosome-derived DNA from patients with early-stage PDAC, with KRAS mutations detected in 66.7% of localized PDAC cases, compared with 45.5% detected through cfDNA. Furthermore, utilizing targeted sequencing, Mizukami *et al* (129) conducted an analysis on the coding regions of 27 cancer-predisposing genes in a cohort consisting of 1,005 patients with PC and 23,705 controls in Japan. Their findings revealed a significant association between pathogenic mutations in BRCA genes and the incidence of PDAC, particularly with regards to BRCA1 and BRCA2 (129). Although BRCA-mutant PDAC constitutes a minority of PDAC cases, recent evidence suggests that BRCA gene testing is indispensable for individuals with a familial history of PDAC, which demonstrated potential in enhancing diagnostic accuracy (130). Future investigations are warranted to explore the detection of minute fragments of BRCA mutations within exosomal DNA, as this approach exhibits potential as an innovative diagnostic technique. The current diagnostic paradigm for PDAC diagnosis, however, exhibits low diagnostic accuracy in this manner. Although there are few studies on this topic, it could be interesting for future investigations.

Proteins. Exosomal proteins, selectively packaged and released by cancer cells, significantly contribute to the communication between tumor cells and their microenvironment. Moreover, specific protein cargoes within exosomes have been implicated in PDAC progression as key regulators in signaling pathways associated with tumor growth, invasion and metastasis. Understanding the dynamic interplay between exosomal proteins and the complex network of molecular events in PDAC is crucial for unraveling the intricacies of this disease and holds promise for developing targeted therapeutic strategies.

Studies have emphasized the potential of GPC1 enriched exosomes for early detection of PDAC (14,131). These exosomes demonstrate superior sensitivity and specificity in distinguishing between PDAC and chronic pancreatitis compared with CA19-9 alone. Non-invasive blood tests can capture these exosomes, presenting a novel approach for early detection of PDAC. Moreover, exosome-based diagnostics overcome genetic variability issues such as Lewis antigen negativity affecting CA19-9 expression and secretion, thereby providing a more comprehensive and precise biomarker system.

In a pivotal study, GPC1-positive circulating exosomes demonstrated an impressive sensitivity of 98.3% and specificity of 86.2%, with a remarkable area under the receiver operating characteristic curve (AUROC) of 0.96, significantly outperforming CA19-9 which exhibited a sensitivity of 78.3% and specificity of 65.5% with an AUROC of 0.82 (P<0.0001) (131). Furthermore, the combination of CA19-9 with the miR-3940-5p/miR-8069 ratio in urine exosomes enhanced diagnostic accuracy, achieving a sensitivity of 93.0% and positive predictive value of 78.4%; when both tests yielded positive results, it resulted in a perfect positive predictive value of 100% (132). These findings underscore the potential utility of exosomal biomarkers not only in surpassing conventional

biomarkers in terms of sensitivity and specificity but also in facilitating non-invasive diagnostic protocols.

Numerous studies have reported the potential of exosomal proteins, including CD44 variant isoform 6/complement C1q binding protein, Claudin-4, epithelial cell adhesion molecule, CD151, lectin galactoside-binding soluble 3 binding protein, histone cluster 2 H2B family member E, histone cluster 2 H2B family member F and others as promising biomarkers for early detection of PDAC (78,133). Additionally, certain exosomal proteins such as New York esophageal squamous cell carcinoma-1 and melanoma antigen gene-A4 remain unidentified but their presence in soft tissue sarcomas through immunostaining techniques suggests their prospective significance in PDAC development and warrants consideration for future screening approaches (134,135).

Exosomes can be isolated from the pancreatic duct fluid and utilized for the diagnosis of patients PDAC (22). Moreover, exosomal proteins have the potential to serve as diagnostic markers for patients with PDAC (32). Exosomes provide a selective enrichment method for cancer-specific material from the diverse pool of circulating non-neoplastic tissue-derived nucleic acids. Additionally, exosomes represent a distinct source of tumor DNA that may complement other sources in liquid biopsy analysis (136). However, it remains unclear which specific types or stages of PDAC can be accurately distinguished using exosomes, which could be an area for future research direction (137,138).

At present, the era of cancer genome profile testing has emerged (139). However, the clinical application of liquid biopsy in PDAC treatment encounters challenges due to the low levels of circulating genetic material observed in patients with PDAC (typically ~0.1% mutant DNA), necessitating the development of ultra-sensitive and reproducible methods for its implementation (140). The limitations associated with cancer genomic testing act as a driving force to propel exosome research forward. By integrating these innovative biomarkers with existing clinical frameworks, significant advancements in early detection and management of PDAC are anticipated, particularly among patients who have been inadequately diagnosed by CA19-9, as illustrated in Table I. Further validation through larger-scale multi-center studies will be crucial to confirm these promising results and explore their utility in longitudinal patient monitoring, potentially enhancing both diagnostic and prognostic outcomes for individuals with PDAC.

5. Exosomes in the treatment of PDAC

The optimal treatment for PDAC is surgical intervention; however, a significant proportion of patients with PDAC (~80%) fail to meet the necessary criteria for surgery, necessitating reliance on conservative pharmacotherapy instead (141,142). Currently, primary treatment options for PDAC are GEM in combination with albumin-bound PTX, GnP, FOLFIRINOX [a regimen comprising 5-fluorouracil (5-FU), leucovorin, irinotecan and oxaliplatin], and modified FOLFIRINOX (mFOLFIRINOX). The Phase III trial demonstrated that the combination of nanoparticle albumin-bound PTX and GEM significantly enhanced overall survival, progression-free survival, and response rate in patients with PDAC. However, it was associated with an increased occurrence of peripheral neuropathy and myelosuppression (143). Conroy *et al* (144) revealed that FOLFIRINOX exhibited a significant survival benefit compared with GEM, albeit with an increased incidence of adverse effects. Furthermore, another study highlighted that the administration of mFOLFIRINOX, as opposed to FOLFIRINOX, may lead to a reduced frequency of Grade 3 or 4 non-hematological adverse events while maintaining a comparable response rate (145).

In the NCCN 2023 guidelines for PDAC, the aforementioned traditional therapies remain commonly used, while new immunotherapy and targeted therapy options have been proposed, including the KRAS inhibitor sotorasib and BRCA inhibitor olaparib (146-148). Although not included in the list of recommended therapies, exosome therapy has shown promise in prolonging survival through its effects on immune response, angiogenesis, drug resistance of tumor cells and other mechanisms.

In PDAC, mutations in KRAS are frequently observed and have been shown to promote aggressive phenotypes (149,150). In the CodeBreaK 100 trial conducted by Strickler *et al* (147), the administration of KRAS G12D inhibitor sotorasib primarily resulted in mild adverse reactions among heavily pretreated populations, with safety outcomes consistent with previous reports from the same trial. KRAS mutations play a crucial role in promoting lymphangiogenesis through exosomes in PC (151). Chang *et al* (152) presented a comprehensive investigation into the role of exosomes in facilitating cell survival driven by KRAS mutations, revealing that KRAS-mutant cells secrete exosomes enriched with the anti-apoptotic protein Survivin. This enrichment not only enhances the survival of neighboring cells but also contributes to the overall therapeutic resistance observed in KRAS-mutant tumors. Their findings suggest that these exosomes act as mediators of intercellular communication, promoting a supportive microenvironment for tumor growth and survival. Furthermore, combining exosomes with other therapies can modulate the pathological progression of PDAC and improve treatment effectiveness. The combination of nano-liposomal irinotecan with FU and folinic acid significantly enhances survival and quality of life in patients with metastatic PDAC post-GEM therapy, highlighting its efficacy and favorable safety profile (153-155).

Several studies have demonstrated that exosomes derived from various cell sources, including immune cells and mesenchymal stem cells, are capable of carrying and delivering a diverse range of biological substances. Additionally, they can specifically target PDAC cells or participate in the progression of PDAC. This phenomenon significantly influences the advancement and invasiveness of PDAC, underscoring its crucial role in the treatment of this disease. Exosomes originating from immune cells such as dendritic cells, T cells and B cells primarily serve vital functions in facilitating the transfer of proteins, nucleic acids and lipids between cells while contributing to intercellular communication and immune regulation (156,157). Meanwhile, exosomes have been demonstrated to possess unique bioactive molecules such as major histocompatibility complex (MHC) and costimulatory molecules, which play a crucial role in mediating immune responses against cancer (158). Current studies have demonstrated that immune exosomes primarily impact the progression of PDAC

Table I. Exosomes in diagnosis of PDAC.

First author, year	Sample	Markers/exosomes	Biological processes	(Refs.)
Hong *et al*, 2022	Serum from healthy individuals/ patients with PDAC	LINC00623	LINC00623 interacts with NAT10 to stabilize oncogenic mRNA via ac4C acetylation.	(126)
Wang *et al*, 2021	Serum from healthy individuals/ patients with PC	miR-125b-3p, miR-122-5p, miR-205-5p	The exosomes in the serum of patients with PC/ patients who succumbed to PC exhibited significant overexpression of three markers.	(121)
Nakamura *et al*, 2022	Serum from healthy individuals/ patients with PDAC	miR-1260a, miR-1260b, miR-141-3p, miR-143-3p, miR-145-5p, miR-148a-3p, miR-200a-3p, miR-200b-3p, miR-200c-3p, miR-216-5p, 216b-5p, miR-217-5p, miR-34a-5p, miR-429, miR-145-3p	The overall diagnostic accuracy was significantly enhanced when CA19-9 levels were utilized in combination.	(102)
Nakamura *et al*, 2019	Serum from healthy individuals/ patients with PC	miR-19b	The diagnostic findings were consistent with the levels of CA19-9.	(122)
Kawamura *et al*, 2019	Serum of patients with PDAC	miR-4525, miR-451a, miR-21	The levels of inverted terminal repeats in venous blood were observed to be elevated compared with those in peripheral blood.	(50)
Wu *et al*, 2020	Serum from healthy individuals/ patients with PC	miR-21, miR-210	The diagnostic potential of miRNA-21 and miRNA-210 levels: 83 and 85%, respectively. Furthermore, accuracy increased to 90%.	(110)
Chen *et al*, 2022	Serum from healthy individuals/ patients with PC	miR-1231	Serum exosome levels in patients with PC decreased significantly compared with healthy controls. Stage I-II patients without distant metastasis or lymph node involvement showed higher exosome miR-1231 levels than stage III-IV or metastatic cases.	(124)
Chen *et al*, 2019	Serum from healthy individuals/ patients with PDAC	miR-21, miR-155	Accuracies: miR-21: 83%, miR-155: 89%, pancreatic juice cytology: 74%. Integration improved accuracy to 91%.	(123)
Yu *et al*, 125	Serum from healthy individuals/ patients with PC	miR-451a	Serum exosome miR-451a levels are elevated in patients with PC with distant metastasis or advanced disease. Significant correlations with clinical stage and distant metastasis exist, and miR-451a expression is responsive to treatment and recurrence.	(125)

Table I. Continued.

First author, year	Sample	Markers/exosomes	Biological processes	(Refs.)
Yadav *et al*, 2018	Serum from healthy individuals/ patients with PC	hsa_circ_0006220, hsa_circ_ 0001666	Hsa_circ_0006220 in serum exosomes of patients with PC associates with CA19-9 and lymph node metastasis. hsa_circ_0001666 correlates with tumor size and CA19-9 levels.	(127)
Mizukami *et al*, 2020	Liquid biopsies from healthy individuals/patients with PDAC	KRAS	The pathogenic mutations in KRAS genes may relate to the occurrence of PDAC.	(129)
Lai *et al*, 2021	Liquid biopsies from healthy individuals/patients with PC	BRCA (especially BRCA 1 and BRCA 2)	The pathogenic mutations in BRCA genes may relate to the occurrence of PC.	(130)
Zhou *et al*, 2018; Moutinho-Ribeiro *et al*, 2022	Serum from healthy individuals/ patients with PDAC	GPC1 + crExos (GPC1 positive exosomal proteins)	GPC1 in serum exosomes of pancreatic cancer patients shows high sensitivity and specificity for early detection of PDAC. Early detection of PDAC, surpasses CA19-9 in sensitivity and specificity	(14, 131)
Yoshizawa *et al*, 2020	Liquid biopsies from healthy individuals/patients with PDAC	CA19-9 combined with miR-3940-5p/miR-8069	Use of CA19-9 and microRNA ratios in urine exosomes for enhanced diagnostic accuracy in PDAC.	(132)
Wu *et al*, 2019	Pancreatic duct fluid from patients with PDAC	Exosomal proteins	Serve as diagnostic markers for PDAC.	(136)
Xie *et al*, 2022	Serum from healthy individuals/ patients with PDAC	CD44 variant isoform 6/ complement C1q binding protein	Exosomal delivery of CD44v6/C1QBP complex to hepatic satellite cells results in activation and fibrosis of liver, which facilitates PDAC liver metastasis.	(133)
Castillo *et al*, 2018	Liquid biopsies from healthy individuals/patients with PDAC	Claudin-4, epithelial cell adhesion molecule, CD151, lectin galactoside-binding soluble 3 binding protein, histone cluster 2 H2B family member E, histone cluster 2 H2B family member F	These biomarkers are part of the PDAC exosomal 'surfaceome' and enhance detection of mutant molecules in PDAC stages, enabling enriched analysis for NGS in liquid biopsies.	(78)

BRCA, breast cancer; CA19-9, carbohydrate antigen 19-9; KRAS, Kirsten rat sarcoma viral oncogene homologue; PC, pancreatic cancer; PDAC, pancreatic ductal adenocarcinoma; GPC1, glypican-1.

by modulating immune responses within the TME. In addition to being secreted by PDAC cells, a majority of existing research (159,160) indicates that exosomes are commonly released by mesenchymal stem cells, which possess convenient accessibility and exhibit both immunogenic and immunomodulatory properties (161). Moreover, several studies have demonstrated the active migration of mesenchymal stem cells to sites of inflammation and their ability to modulate immune responses. Furthermore, it has been observed that paracrine exosomes predominantly convey biological information rather than direct cell contact (162,163). For example, umbilical cord stem cells possess robust potential in regulating tissue differentiation and regeneration due to their strong stem cell capacity (164). The exosomes can additionally regulate the TME by exerting regulatory control over angiogenesis and proliferation of PDAC cells within the TME (165). Adipose mesenchymal stem cells are more likely to play a pivotal role in immunomodulation and anti-inflammatory processes, as their exosomes have the ability to regulate the expression of interleukin 6, interleukin 10, and tumour necrosis factor alpha, thereby participating in immune modulation and inflammation regulation *in vivo* (166,167). For instance, Liu *et al* (168) demonstrated that exosomes derived from adipose-derived mesenchymal stem cells can mitigate oxidative stress, inflammation and infiltration of microglial cells through the activation of the silent information regulator sirtuin 1 pathway. Therefore, exosomes derived from diverse cellular origins exert a regulatory influence on the progression of PDAC by modulating angiogenesis and mitigating the inflammatory response.

Exosomes derived from antigen-presenting cells, such as dendritic cells and macrophages, play a pivotal role in transporting and presenting functional MHC peptide complexes to modulate antigen-specific T cell responses. This underscores their protective function in attenuating inflammation or enhancing immune responses (169). In the context of cancer vaccine development, computational structural modeling has been employed to predict immunogenic neoepitopes for cancer vaccines, with a specific focus on targeting neoantigens predicted using MHC binding algorithms (170).

Tumor cells typically require the production of angiogenic growth factors to establish their vascular network, among which cytokines such as vascular endothelial-derived growth factor (VEGF), and roundabout guidance receptor 1 (ROBO1) play crucial roles in the process of angiogenesis within PDAC (171-174). Lee *et al* (175) and Pakravan *et al* (176) reported that exosomes derived from mesenchymal stromal cells (MSCs) can selectively target tumor cells by utilizing miR-16 or miR-100, thereby modulating the mechanistic target of rapamycin/hypoxia inducible factor 1-alpha signaling pathway to suppress intracellular VEGF expression and consequently attenuate the angiogenic potential of tumor cells.

In addition to MSCs, exosomes derived from PDAC cells may also possess corresponding anti-angiogenic mechanisms. Research has demonstrated that miR-29b originating from PDAC cells can downregulate VEGF expression and diminish the migration rate and angiogenesis capability of vascular endothelial cells, primarily by suppressing ROBO1 and SLIT-ROBO Rho GTPase-activating protein 2, thereby attenuating the angiogenesis induced by PDAC cells (173).

The TME is a complex and diverse ecosystem comprising cancer cells, fibroblasts, adipocytes, endothelial cells and mesenchymal stem cells (177). The exosomes can also be derived from CAFs and other stromal cells within the TME (62). CAFs, a heterogeneous stromal cell population with diverse cellular origins, phenotypes and functions, represent one of the significant sources of exosomes within the TME (178,179). For example, CAFs can utilize the miR-135b5p/Forkhead box transcription factor O1 axis to promote the formation of new blood vessels for cancer cells (180). Additionally, CAFs have the ability to induce expression of lnc HOTAIR, which facilitates tumor metastasis by promoting EMT (181,182). Moreover, exosomes derived from CAFs enhance tumor drug resistance and self-renewal capabilities of cancer stem cells by providing them with mitochondrial genomes that improve oxidative phosphorylation and mitochondrial metabolism (183). These exosomes also contain essential metabolites such as amino acids, lipids and tricarboxylic acid cycle intermediates that are utilized by cancer cells during periods of nutritional deficiency or stress. Furthermore, CAFs contribute to tumor resistance against anticancer treatments through their secretion of multiple exosomes (184). For instance, these exosomes can activate retinoic acid inducible gene 1 protein signaling in cancer cells or stimulate NOTCH3 signaling on cancer cells via Jagged 1 present on CAFs. The collaboration between these pathways ultimately leads to enhanced resistance against radiation therapy and chemotherapy (185). By targeting the aforementioned mechanisms, pharmaceutical interventions can be developed for the treatment of PDAC.

Specialized adipocytes known as cancer-associated adipocytes (CAAs) play a significant role in various tumor types, including BRCA, ovarian cancer, PDAC, kidney, gastric and colon cancers (186). These CAAs interact with tumor cells, leading to alterations in their properties and functions. The impact of specific miRNAs, such as miR-144, miR-126 and miR-155, present in exosomes on tumor growth, has been observed to be mediated through their targeted influence on adipocytes (187). Moreover, in the presence of tumor cells, adipocytes upregulate exosomal miRNA-155 levels to attract macrophages and facilitate their differentiation into TAMs that support tumor growth (188-190). Additionally, CAA secretion of visfatin has been shown to induce M2 phenotype polarization in macrophages that promotes malignancy and enhances glycolysis.

The exosomes can also originate from normal fibroblast-like mesenchymal cells and bear distinct markers of PDAC tumor cells (191,192). Therefore, exosomes within the TME can originate from a diverse range of cellular sources, extending beyond MSCs and PDAC cells, including CAFs, CAA and tumor-associated endothelial cells (193). Exosomes from these sources have been shown to be related to cancer metabolism and drug resistance in pan-cancer studies, and it may be possible to diagnose PDAC cells drug resistance through them, but the specific mechanism has not been clearly studied (10,194).

The progression of PDAC is intricately linked to the migration, invasion and metastasis of PDAC cells (195). A disintegrin and metalloproteinase domain-containing 9 protein is a relevant protein implicated in the advancement, metastasis and unfavorable prognosis of tumors (196). Shang *et al* (197)

discovered that miR-1231 was commonly employed as one of the diagnostic markers for early-stage PDAC progression in previous studies. However, their animal experiments revealed that MSC exosomes carrying miR-1231 exerted a negative regulatory effect on the migration, invasion and adhesion of PDAC cells, thereby effectively inhibiting PDAC activity (197). The study conducted by Yao *et al* (198) proposed that circular RNA present in mesenchymal stem cell exosomes may play a pivotal role in the progression of PDAC. Through comprehensive transcriptome gene sequencing and heat map analysis, circ-0030167 was found to specifically target the expression of WNT inhibitory factor-1 in PDAC cells by interacting with miR-338-5p, thereby effectively suppressing the aberrant activation of the Wnt signaling pathway. Consequently, this regulatory mechanism exerts inhibitory effects on both proliferation and migration processes in PDAC cells.

Once tumor cells develop drug resistance, the effectiveness of chemotherapy drugs will be significantly diminished. Preliminary experiments have indicated that the drug resistance in tumor cells is associated with the activation of calmodulin-dependent kinases/Raf/MEK/ERK signaling pathway, and *in vivo* exosomes derived from MSCs may play a crucial role in the mechanism underlying tumor cell dormancy (199-201). The findings of Ono *et al* (202) demonstrated that MSCs exosomes transferred miR-23b to tumor cells, thereby inducing tumor dormancy through the inhibition of MARCKS expression. These results are consistent with those reported by Yang *et al* (203). They suggested that *in vivo*, MSCs could induce tumor cell quiescence and enhance drug resistance through dormancy, highlighting the significance of exosomes as crucial targets for reducing tumor drug resistance. Expanding on this hypothesis, Fu *et al* (204 and Fan *et al* (205) conducted *in vitro* experiments to validate the substantial impact of exosome miR-520-5p and Ephrin type-A receptor 2 (EphA2) on GEM resistance and transfer of drug resistance in PDAC cells. However, ongoing exosome research focused on exosomes aimed at mitigating drug resistance in PDAC necessitates further elucidation of the influence of drug resistance and its generation mechanism.

The precise targeting capabilities of exosomes suggest potential for personalized treatment strategies in PDAC. For instance, an optimized approach to exploit variable biomarker expressions is being developed in PDAC using a specialized formulation of exosomes loaded with erastin, which selectively targets triple-negative BRCA cells by leveraging the overexpression of folate receptors (206,207).

Exosomes derived from cancer cells have been employed not only for efficient drug delivery but also as nanoanalytical contrast agents, particularly in the diagnosis and monitoring of PDAC. Comparative investigations conducted on other gastrointestinal malignancies reveal a significant underutilization of such diagnostic applications in gastric and colon cancers, where research predominantly focuses on fundamental cellular interactions and molecular cargo analysis (208).

Furthermore, the novel use of milk-derived exosomes for the oral delivery of hydrophobic drugs represents a significant breakthrough with potential applications in gastrointestinal cancer treatments (209). In PDAC, where invasive interventions are prevalent, the development of oral exosome-based therapies could profoundly transform treatment strategies by offering less invasive and more patient-centric alternatives.

While significant progress has been made in exosome research for PDAC, there is a pressing need for more extensive investigations into diagnostic and therapeutic applications in other gastrointestinal cancers. The distinct challenges posed by PDAC, characterized by its aggressive nature and often late-stage diagnosis, necessitate tailored approaches that may not be directly applicable to less aggressive or differently behaving tumors. Nevertheless, the fundamental principles derived from exosome research can inform broader strategies in gastrointestinal oncology, fostering interdisciplinary innovations and potentially identifying universal or cancer-specific therapeutic targets.

To enrich the discourse on the role of exosomes in the prognosis of PDAC, a comprehensive compilation about various exosomal markers and their associated biological processes is presented in Table II. For instance, exosomes derived from PC cells exhibit markers such as c-Met and PD-L1, which are implicated in promoting invasive expansion and immune evasion, thereby adversely affecting prognosis (210). Additionally, exosomes from malignant ascites of patients with PC, characterized by the presence of CD133 and other cancer stem cell markers, contribute to the establishment of a TME that facilitates tumor growth, metastasis and angiogenesis (211). These processes further induce immune suppression and drug resistance, ultimately impacting patient outcomes.

In the context of blood plasma, exosomal miR-451a has been identified as a significant independent factor for overall survival and disease-free survival in PDAC, regulating key biological processes such as proliferation, invasion and metastasis (212). Similarly, EphA2 found in serum exosomes correlates positively with tumor stage and reduced survival rates, highlighting its role in cancer cell proliferation and invasion (213).

Moreover, the upregulation of miR-23b-3p in serum exosomes from patients with PDAC promotes cell proliferation, migration and invasion, demonstrating its association with CA19-9 levels, a common tumor marker (214). The involvement of miR-3607-3p, enriched in exosomes from natural killer cells, suggests a potential prognostic marker, as low levels of this miRNA are linked to poor prognosis in PDAC (94).

Exosomal miR-222 has been shown to enhance cell proliferation and invasion by downregulating p27 through the miR-222/PPP2R2A/AKT pathway, indicating its relevance in PC incidence and prognosis (215). Additionally, miR-106b and miR-146a contribute to GEM resistance in cancer cells, with miR-146a promoting epithelial cell proliferation and survival upon transfer to recipient cells (216,217).

Finally, the long-term exposure of PDAC cells to GEM leads to the upregulation of miR-155, which promotes anti-apoptosis and exosome secretion, thereby facilitating chemoresistance. This miRNA is also transferred to other PDAC cells, inducing functional changes that may impact treatment outcomes (218). MiR-212-3p in PDAC exosomes has been shown to suppress immune responses by impairing $CD4^+$ T cell activation, fostering an immunotolerant microenvironment (219). Furthermore, miR-501-3p, derived from M2 macrophage exosomes, inhibits transforming growth factor beta receptor

Table II. Exosomes in prognosis of PDAC.

First author, year	Sample	Markers/exosomes	Biological processes	(Refs.)
Wei *et al*, 2021	PC cells	c-Met, PD-L1	Exosomes promote invasive expansion and immune evasion in PC via c-Met and PD-L1, impacting prognosis.	(213)
Chen *et al*, 2017	Malignant ascites patients with PC	CD133	Exosomes with CD133 and other cancer stem cell markers create a tumor microenvironment in the peritoneal cavity, promoting PC progression via growth, metastasis and angiogenesis. They also induce immune suppression, drug resistance and epithelial-mesenchymal transition, impacting prognosis.	(214)
Li *et al*, 2018	Blood plasma	miR-451a	Exosomal miR-451a in PDAC regulates gene expression and biological processes (proliferation, invasion and metastasis). It is a significant independent factor for overall survival and disease-free survival.	(215)
Fang *et al*, 2018	Serum from healthy individuals/patients with PC	Ephrin type-A receptor 2 (EphA2)	EphA2 promotes cancer cell proliferation and invasion. Exo-EphA2 in serum mirrors exosomal levels. Positive correlation with PC tumor stage and reduced survival rates observed.	(216)
Richards *et al*, 2017	Serum from healthy individuals/patients with PC	miR-23b-3p	miR-23b-3p upregulation in PC serum promotes cell proliferation, migration and invasion. Detected in extracellular vesicles, it correlates positively with CA19-9 levels.	(217)
Sun *et al*, 2019	Natural killer cells	miR-3607-3p	miR-3607-3p enriched in natural killer cell EVs transfers to PC cells. Low levels linked to poor prognosis. Inhibits PC cell proliferation, migration and invasion *in vitro*.	(94)
Mikamori *et al*, 2017	Serum from healthy individuals/patients with PC	miR-222	Exo-miR-222 from tumors downregulates p27 via the miR-222/PPP2R2A/AKT pathway. Enhances cell proliferation, invasion and metastasis. Plasma exo-miR-222 levels link to PC incidence and prognosis.	(218)
Batista *et al*, 2019	CAFs	miR-106b	The promotion of gemcitabine resistance in cancer cells by miR-106b is achieved through direct targeting of tumor protein 53-induced nuclear protein-1.	(219)
Yin *et al*, 2019	CAFs	miR-146a	The expression of Snail and miR-146a in EVs from patients with PC is increased by gemcitabine treatment. These EVs promote epithelial cell proliferation and survival upon transfer to recipient cells.	(220)
Zhou *et al*, 2021	Serum from healthy individuals/patients with PDAC	miR-155	Long-term gemcitabine exposure in PDAC cells upregulates miR-155, promoting anti-apoptosis and exosome secretion for chemoresistance. Exosomes deliver miR-155 to other PDAC cells, inducing functional changes.	(221)
Li *et al*, 2020	Serum from healthy individuals/patients with PC	miR-212-3p	miR-212-3p in PC exosomes suppresses regulatory factor X associated protein, reducing DC major histocompatibility complex class II and impairing $CD4^+$ T cell activation, fostering an immunotolerant PC microenvironment.	(222)
Kamerkar *et al*, 2017	M2 macrophage	miR-501-3p	PDAC development facilitated by M2 macrophage exo-miR-501-3p via transforming growth factor-beta pathway inhibition of transforming growth factor beta receptor 3.	(223)

CA19-9, carbohydrate antigen 19-9; PC, pancreatic cancer; PDAC, pancreatic ductal adenocarcinoma; EphA2, Ephrin type-A receptor 2; CAF, cancer-related fibroblasts; EVs, extracellular vesicles; miR, microRNA.

3, disrupting the TGF-β signaling pathway and promoting a pro-TME that facilitates PDAC development (220).

To help with a more comprehensive understanding, exosomal markers in the treatment of PDAC have also been summarized in Table III. Notably, exosomes derived from bone marrow mesenchymal stem cells have been shown to effectively deliver chemotherapeutic agents such as oxaliplatin and siRNA to tumors, thereby enhancing antitumor immunity and prolonging the circulation of therapeutic cargo (221). Furthermore, fibroblast-derived exosomes have been implicated in promoting PC cell survival through the release of mRNA and miRNA, with the inhibition of exosome secretion via GW4869 leading to a reversal of drug resistance and suppression of tumor growth (217).

Additionally, miR-1231 from bone marrow mesenchymal stem cells has demonstrated a suppressive impact on PC cell proliferation, migration, invasion and adhesion (197). Autologous exosomes secreted by PC cells have been utilized for targeted delivery of GEM, highlighting the potential of exosomes as vehicles for chemotherapeutic agents (222). The engineering of exosomes to deliver RNA specifically targeting oncogenic KRASG12D has also shown promise in achieving targeted inhibition of PC cells driven by this mutation (223).

Moreover, the combination of tumor-exosome-loaded dendritic cells with cytotoxic drugs has been reported to enhance T cell recovery and improve survival outcomes (224). Chlorin e6-loaded tumor-derived re-assembled exosomes have enabled the integration of photodynamic therapy and immune therapy, resulting in the generation of reactive oxygen species and enhanced cytokine release (225). Ongoing research into exosomal proteins from PANC-1 cells aims to assess their potential in activating dendritic cells and cytokine-induced killer cells, further exploring agonists for their activation (226). Finally, the application of exosomes in the treatment and diagnosis of PDAC was summarized, as depicted in Fig. 2.

6. The potential role of exosomes as drug delivery tools

The exosomes, serving as endogenous carriers of molecular information between cells, possess the characteristics of small size and excellent biocompatibility (227). Exosomes can serve as a versatile drug carrier capable of encapsulating diverse compounds, including small molecule chemical drugs, proteins and nucleic acids (228,229). The use of exosomes as drug carriers is advantageous due to their ability to preserve the biological activity of drugs within the membrane, while also avoiding any immune response *in vivo*. This renders them more suitable for delivery compared with traditional nano-delivery carriers such as liposomes, thus making it a prominent area of research in tumor therapy (230,231).

The low immunogenicity and high tissue permeability of exosomes confer significant advantages for the delivery of small molecule drugs, such as siRNA and miRNA. Previous studies have demonstrated that exosomes derived from 293 cells, when loaded with exogenous siRNA, can effectively inhibit tumor cell growth by silencing the human epidermal growth factor receptor 2 gene (232). The study conducted by Zuo *et al* (233) employed ultrasound for the transfection of miR-34a into exosomes. The findings demonstrated that ExomiR-34a effectively traversed the cell membrane and downregulated the expression of its target gene BCL-2, thereby inducing apoptosis in PDAC cells. Moreover, it significantly impeded tumor proliferation *in vivo* (233). The miRNA-145-5p functions as a potent tumor suppressor, exhibiting a significant correlation with the extent of macrophage infiltration. Ding *et al* (234) proposed that its dysregulation is closely associated with aberrant proliferation and invasion of PDAC cells. By constructing vectors for engineering MSC exosomes, exogenous miR-145-5p was utilized in animal experiments pertaining to the progression of PDAC. The findings demonstrated that exosomes containing miR-145-5p significantly impeded the *in vivo* growth of PDAC cells by inducing cell cycle arrest and augmenting the apoptosis rate of these cells.

Chemical drugs often induce a variety of allergic or complication reactions due to their low targeting efficacy (235). However, MSC exosomes possess inherent tumor-targeting properties derived from their parental cells, and the abundance of proteins on their membrane provides numerous targeting ligands and chemical modification sites for engineering exosomes specifically designed to target tumor cells (236). Therefore, exosomes derived from MSCs present a promising solution to overcome this challenge. Pascucci *et al* (237) conducted experiments to investigate the therapeutic effects of MSC exosomes loaded with PTX, which were generated through co-culture method. The results demonstrated that PTX-loaded exosomes exhibited a significant inhibitory effect on the proliferation activity of PDAC cells compared with PTX alone. Furthermore, in line with this hypothesis, several studies have also confirmed the efficacy of MSC exosomes loaded with GEM, a standard chemotherapy drug for PDAC. *In vitro* experiments have revealed a certain degree of growth inhibition in PDAC cells, and from a pharmacological perspective, local administration of MSC exosomes loaded with GEM can significantly enhance drug concentration. Consequently, it is possible to design a more effective targeting strategy for PDAC lesion areas (238). The effect of GEM-loaded MSCs exosomes on systemic toxicity and efficacy was validated by Li *et al* (222) through the establishment of a PDAC animal model (222). The results demonstrated that EXO-GEM induced minimal harm to mice compared with direct injection of GEM, while significantly suppressing tumor proliferation without any indications of tumor recurrence in mice. Considering the common clinical application of combined therapies involving GEM and PTX, Zhou *et al* (160) constructed MSCs exosomes loaded with both GEM and PTX for PDAC treatment. Compared with the chemo-drug group, the MSCs exosomes-chemo-drug group exhibited greater persistence and targeting, resulting in higher overall survival rates compared with other control groups.

It is noteworthy that the clearance of exosomes by pancreatic and immune cells can exert an influence on the TME and thereby impact the progression or inhibition of PDAC. This aspect holds particular significance in cases where exosomes are employed as drug delivery vehicles. Kamerkar *et al* (223) have reported that the presence of CD47 on exosomes hampers their clearance, rendering them more adept at evading phagocytic elimination compared with liposomes. This evasion mechanism is partly mediated by cluster of differentiation 47-signal-regulatory protein alpha interactions on exosomes, which aid in circumventing host immune surveillance signals known as ‘don't eat me’ signals (223). The presence of plasma

Table III. Exosomal markers in treatment of pancreatic ductal adenocarcinoma.

First author, year	Sample	Markers/exosomes	Biological processes	(Refs.)
Kamerkar *et al*, 2017	Bone marrow mesenchymal stem cells	Galectin-9 siRNA, Oxaliplatin	Exosomes delivered oxaliplatin and siRNA to tumors, protecting cargo genes, inducing anti-tumor immunity, prolonging circulation, and treating PANC-02 tumors effectively.	(223)
Batista *et al*, 2019	Fibroblasts	GW4869	Exosomes promote PC cell survival via mRNA/miRNA release during chemo. GW4869 reduces exosome secretion, reversing resistance and suppressing tumor growth via marker overexpression.	(219)
Ji *et al*, 2015	Bone marrow mesenchymal stem cells	miR-1231	miR-1231 from bone marrow mesenchymal stem cells inhibits PC cell proliferation, migration, invasion and adhesion, showing suppressive impact on PC.	(199)
Xiao *et al*, 2017	Autologous exosomes secreted by PC cells	Gemcitabine	The therapeutic effects of exosomes are achieved through targeted delivery of the chemotherapeutic drug gemcitabine for the treatment of PC.	(224)
Jang *et al*, 2021	Fibroblast-like mesenchymal cells	Oncogenic KRAS	Engineer exosomes to deliver short interfering RNA or short hairpin RNA specifically targeting oncogenic KRASG12D, thereby achieving targeted inhibition of PC cells driven by oncogenic KRAS.	(225)
Que *et al*, 226	UNKC6141 cells	Tumor-exosome-loaded dendritic cells	Combining dendritic cells-vaccinated exosomes with cytotoxic drugs enhances T cell recovery, improving survival.	(226)
Duan *et al*, 2021	Tumor cells	Chlorin e6-loaded tumor-derived re-assembled exosom	Chlorin e6-loaded tumor exosomes enable combined Photodynamic therapy and immune therapy, generating reactive oxygen species and enhancing cytokine release.	(227)
Moon and Chang, 2022	PANC-1 cells	Exosomal proteins	Research on miRNA-depleted exo-proteins for dendritic cells/cytokine-induced killer cells treatment and activation assessment ongoing. Agonists explored for PC-137 dendritic cells/cytokine-induced killer cells' activation.	(228)

KRAS, Kirsten rat sarcoma viral oncogene homologue; miR or miRNA, microRNA; siRNA, small interfering RNA; PC, pancreatic cancer.

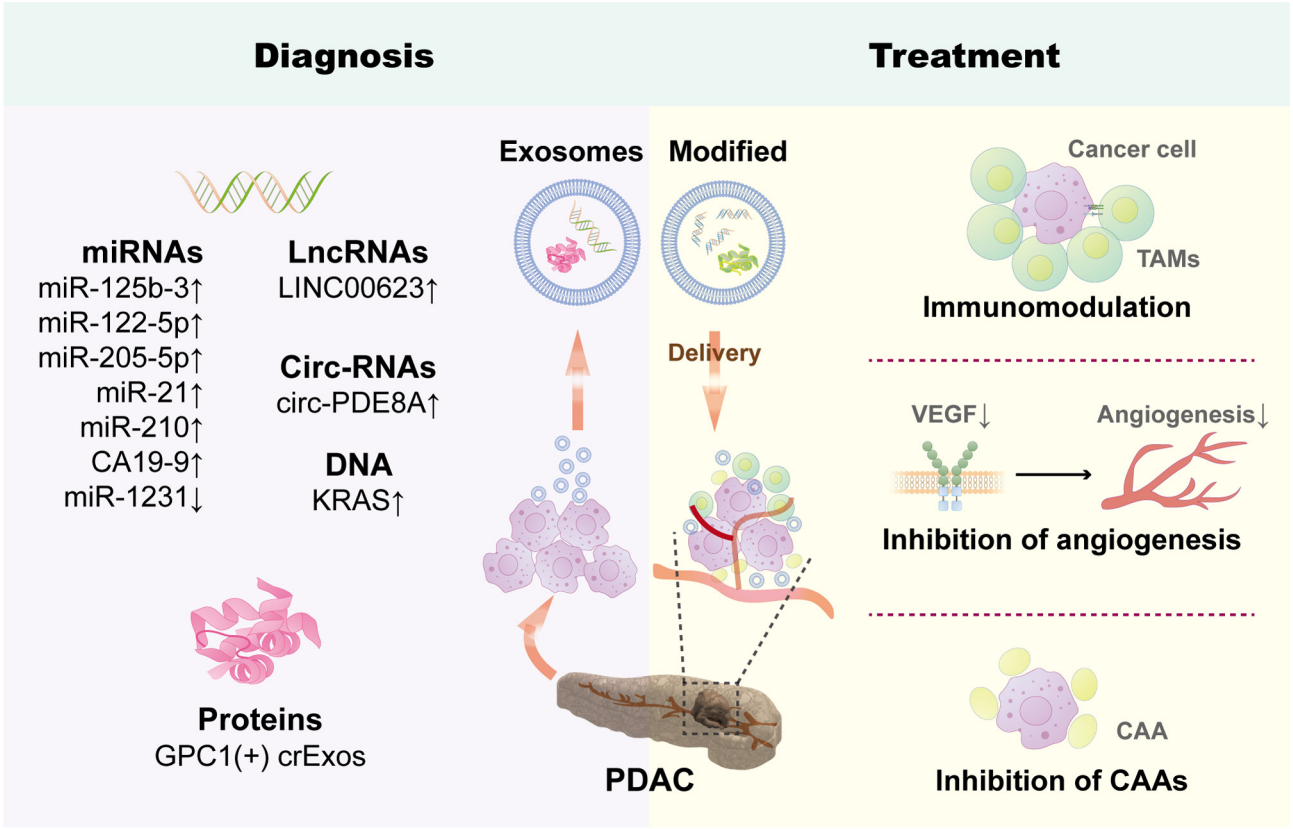

Figure 2. Applications of exosomes for PDAC. During the progression of PDAC, exosomes are released by malignant tumor cells. Through screening exosomes for various types of bioactive molecules, such as mRNA, miRNA, lncRNA, circRNA, DNA and proteins carried by early liquid biopsy, the accuracy and efficacy of PDAC diagnosis can be enhanced. Exosomes derived from diverse cell sources possess the ability to transport various biological substances and specifically target PDAC cells or contribute to PDAC advancement. The mechanisms involved encompass immunomodulation, angiogenesis inhibition and suppression of CAAs. These findings underscore its significant role in the treatment of this disease. PDAC, pancreatic ductal adenocarcinoma; miRNA or miR, microRNA; lncRNA, long non-coding RNA; circRNA, circular RNA; CAAs, cancer-associated adipocytes; GPC1, glypican-1; TAMs, tumor-associated macrophages; LINC, long intergenic non-coding.

membrane-like phospholipids and membrane-anchored proteins in exosomes may contribute to their reduced clearance from the circulation (239-241). Although CD47 does not play a significant role in facilitating the entry of exosomes into pancreatic cells, the enhanced macropinocytosis observed in KRAS-mutant cancer cells promotes their uptake of exosomes (242,243). Further investigation is warranted to explore whether exosomes can evade lysosome-dependent degradation of their cargo by utilizing macropinocytosis as an entry mechanism.

Moreover, comprehensive assessment of the *in vivo* efficacy and safety of these engineered exosomes involves a diverse range of techniques. These encompass nanoparticle tracking analysis for validating size uniformity and particle concentration, flow cytometry for confirming surface marker expression and ensuring accurate cellular sourcing, as well as *in vivo* assays for directly measuring therapeutic impact and safety profiles (244). Rigorous testing is essential to advance these platforms towards clinical applications.

7. Implications of bacterial exosomes in PDAC

Intriguingly, the conventional notion of the pancreas as a sterile environment has been recently challenged by suggesting the presence of bacteria capable of secreting exosomes (245). These bacterial exosomes have emerged as potential contributors to the dynamics of PDAC, exerting influence on tumor progression and drug resistance (246). Despite their significant implications, this microbial aspect remains understudied in relation to PDAC, highlighting a critical gap in current research. Exploring the intricate interplay between bacterial exosomes and pancreatic tumors opens up new avenues for comprehending the multifaceted nature of this malignancy.

From a clinical and anatomical perspective, there is no direct physical connection between the pancreas and the gut microbiota; therefore, the pancreas is considered to be a sterile tissue (247,248). However, microorganisms can migrate to the pancreas through the bile duct in the digestive tract (249,250). Numerous studies have demonstrated a robust correlation between the composition of oral, gastrointestinal, fecal and organ-specific (pancreatic) microbiota and PDAC (251). The development of periodontal disease in the oral cavity has been associated with several key pathogenic bacteria, including *Porphyromonas gingivalis*, *Fusobacterium*, *Streptococcus mitis* and *Neisseria elongata* (252). The secretion of peptidyl-arginine deiminase by *Porphyromonas gingivalis* is hypothesized to induce mutations in the KRAS and tumor suppressor p53 genes, thereby degrading arginine metabolism (253). The oral administration of fluorescently-labeled *Enterococcus faecalis* to wild type mice in an experiment

resulted in the observation of fluorescence in the pancreas, indicating bacterial migration from the gastrointestinal tract to the pancreas (254). The ability of bacteria to transfer intracellular materials outside the body via exosomes suggests that targeting bacterial exosomes could be a potential therapeutic approach for treating PDAC (255).

8. Challenges and limitations

The journey from laboratory discovery to clinical application is always challenging, and this holds true for PDAC-specific exosomes as well. In this arduous process, the initial crucial step involves isolating high-quality PDAC-specific exosomes. Recent advancements in microfluidic technologies have facilitated the efficient capture of exosomes from small blood volumes using highly specific antibodies (34). Although this method has the potential to enable early screening using simple fingertip samples from patients, there are significant challenges in scaling up the technology for clinical use due to its complexity, costliness and requirement for specialized equipment (34).

The second challenge lies in the safety of modified exosomes. Numerous modified exosomes have been utilized for targeted delivery of therapeutic agents such as small molecule drugs, nucleic acids and proteins to cancer cells. A comprehensive assessment of the ethical and legal implications associated with these innovative treatments is imperative to ensure patient safety under appropriate therapeutic conditions. For instance, early clinical trials have demonstrated the potential efficacy of mesenchymal stem cell-derived exosomes loaded with therapeutic siRNA targeting the mutant KRAS-G12D gene for treating metastatic PDAC. However, concerns exist regarding the inadvertent promotion of tumor growth and metastasis by these vesicles (34).

Moreover, there are certain limitations associated with engineering exosomes. Modifications inevitably affect the natural properties and delivery efficacy of exosomes, thus achieving a balance between harnessing their complete therapeutic potential while preserving inherent functionalities remains a key challenge. Additionally, production and purification processes require high efficiency and reproducibility to ensure a pure population of exosomes. However, conventional methods such as differential centrifugation often yield preparations contaminated with protein aggregates and other cellular debris (256). This highlights the necessity of developing advanced and scalable purification techniques that comply with clinical standards. Continuous innovation in exosome isolation and purification technologies, along with comprehensive clinical trials to evaluate the safety and efficacy of exosome-based interventions, is crucial for addressing these challenges and limitations.

In addition to PC, gastrointestinal cancers such as gastric, colorectal and liver cancers have also emerged as significant areas of interest in exosomal research. Numerous miRNAs, lncRNAs, circRNAs and proteins have been identified as potential diagnostic and prognostic biomarkers or therapeutic targets for gastroenterological malignancies (257-259). Due to its high global mortality rate, PC has garnered extensive attention from researchers aiming to develop diverse engineered exosomes that could facilitate the exploration of novel opportunities for generating clinical-grade exosomal technologies and drugs.

Therefore, it is imperative to overcome the challenges and limitations in order to fully exploit the potential of exosomes in PDAC diagnosis and treatment. This will facilitate more efficacious disease management and establish a precedent for broader application of exosomal therapies in the field of oncology.

9. Conclusion

PDAC is the most prevalent and lethal disease among solid malignant tumors. Conventional tumor drugs used for treatment often lead to drug resistance without any targeted alternatives available, resulting in a challenging situation for PDAC diagnosis and treatment. In addition to replacing existing biomarkers for PDAC diagnosis, exosomes can enhance the accuracy rate by combining detection methods or serving as an auxiliary tool alongside existing techniques such as endoscopy, ultrasound detection and imaging. Moreover, exosomes can differentiate between different stages of PDAC progression based on their content, potentially playing a broader role in clinical diagnosis and treatment. Additionally, due to their intercellular communication capabilities along with their safety profile and targeting abilities, exosomes hold potential as a novel therapeutic option. Their unique lipid structure also enables them to act as efficient drug delivery vehicles that prolong drug action time within the body while reducing toxicity levels when treating PDAC and other cancers. However, current diagnostic and therapeutic applications involving exosomes are still limited to preclinical experimental stages; thus, further comprehensive clinical research studies and trials are warranted. It is anticipated that exosomes will become an effective tool or method for precise diagnosis and treatment of PDAC in the future.

Acknowledgements

Not applicable.

Funding

The present study was supported by the National Undergraduate Training Programs for Innovation and Entrepreneurship (grant no. 202411065052), the Shandong undergraduate training programs for innovation and entrepreneurship (grant nos. S202311065054 and S202411065020) and the Qingdao Medical and Health Research Guidance Project (grant nos. 2022-WJZD108 and 2023-WJZD106).

Availability of data and materials

Not applicable.

Authors' contributions

Each author has made substantial contributions to the conception of the study. XCL, XZW, GB, XXL, ZRG, ZSZ, TYH, JPZ, HJZ, XYL and ZJL drafted the manuscript. FFG, LLD and WHZ substantively revised the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Cancer Genome Atlas Research Network. Electronic address: Andrew_aguirre@dfci.harvard.edu; Cancer Genome Atlas Research Network. Integrated Genomic Characterization of Pancreatic Ductal Adenocarcinoma. Cancer Cell 32: 185-203. e113, 2017.
2. Klein AP: Pancreatic cancer epidemiology: Understanding the role of lifestyle and inherited risk factors. Nat Rev Gastroenterol Hepatol 18: 493-502, 2021.
3. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I and Jemal A: Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 74: 229-263, 2024.
4. Luo G, Jin K, Deng S, Cheng H, Fan Z, Gong Y, Qian Y, Huang Q, Ni Q, Liu C and Yu X: Roles of CA19-9 in pancreatic cancer: Biomarker, predictor and promoter. Biochim Biophys Acta Rev Cancer 1875: 188409, 2021.
5. Carmicheal J, Patel A, Dalal V, Atri P, Dhaliwal AS, Wittel UA, Malafa MP, Talmon G, Swanson BJ, Singh S, *et al*: Elevating pancreatic cystic lesion stratification: Current and future pancreatic cancer biomarker(s). Biochim Biophys Acta Rev Cancer 1873: 188318, 2020.
6. Bestari MB, Joewono IR and Syam AF: A quest for survival: a review of the early biomarkers of pancreatic cancer and the most effective approaches at present. Biomolecules 14: 364, doi: 10.3390/biom14030364, 2024.
7. Yang J and Xu R: Early screening and diagnosis strategies of pancreatic cancer: A comprehensive review. Cancer Commun (Lond) 41: 1257-1274, 2021.
8. Jia Y, Chen Y, Wang Q, Jayasinghe U, Luo X, Wei Q, Wang J, Xiong H, Chen C, Xu B, *et al*: Exosome: Emerging biomarker in breast cancer. Oncotarget 8: 41717-41733, 2017.
9. Han QF, Li WJ, Hu KS, Gao J, Zhai WL, Yang JH and Zhang SJ: Exosome biogenesis: Machinery, regulation, and therapeutic implications in cancer. Mol Cancer 21: 207, 2022.
10. Costa-Silva B, Aiello NM, Ocean AJ, Singh S, Zhang H, Thakur BK, Becker A, Hoshino A, Mark MT, Molina H, *et al*: Pancreatic cancer exosomes initiate pre-metastatic niche formation in the liver. Nat Cell Biol 17: 816-826, 2015.
11. Awadallah NS, Shroyer KR, Langer DA, Torkko KC, Chen YK, Bentz JS, Papkoff J, Liu W, Nash SR and Shah RJ: Detection of B7-H4 and p53 in pancreatic cancer: Potential role as a cytological diagnostic adjunct. Pancreas 36: 200-206, 2008.
12. Bausch D, Mino-Kenudson M, Fernández-Del Castillo C, Warshaw AL, Kelly KA and Thayer SP: Plectin-1 is a biomarker of malignant pancreatic intraductal papillary mucinous neoplasms. J Gastrointest Surg 13: 1948-1954, 2009.
13. Yu W, Ma Y, Shankar S and Srivastava RK: Role of SATB2 in human pancreatic cancer: Implications in transformation and a promising biomarker. Oncotarget 7: 57783-57797, 2016.
14. Zhou CY, Dong YP, Sun X, Sui X, Zhu H, Zhao YQ, Zhang YY, Mason C, Zhu Q and Han SX: High levels of serum glypican-1 indicate poor prognosis in pancreatic ductal adenocarcinoma. Cancer Med 7: 5525-5533, 2018.
15. Padden J, Ahrens M, Kälsch J, Bertram S, Megger DA, Bracht T, Eisenacher M, Kocabayoglu P, Meyer HE, Sipos B, *et al*: Immunohistochemical markers distinguishing cholangiocellular carcinoma (CCC) from pancreatic ductal adenocarcinoma (PDAC) discovered by proteomic analysis of microdissected cells. Mol Cell Proteomics 15: 1072-1082, 2016.
16. Herreros-Villanueva M and Bujanda L: Non-invasive biomarkers in pancreatic cancer diagnosis: What we need versus what we have. Ann Transl Med 4: 134, 2016.
17. Brezgyte G, Shah V, Jach D and Crnogorac-Jurcevic T: Non-invasive biomarkers for earlier detection of pancreatic Cancer-A comprehensive review. Cancers (Basel) 13: 2021.
18. Zheng H, Liang X, Liu B, Huang X, Shen Y, Lin F, Chen J, Gao X, He H, Li W, *et al*: Exosomal miR-9-5p derived from iPSC-MSCs ameliorates doxorubicin-induced cardiomyopathy by inhibiting cardiomyocyte senescence. J Nanobiotechnology 22: 195, 2024.
19. Chen YX and Cai Q: Plant Exosome-like nanovesicles and their role in the innovative delivery of RNA therapeutics. Biomedicines 11: 1806, 2023.
20. Tamura R, Balabanova A, Frakes SA, Bargmann A, Grimm J, Koch TH and Yin H: Photoactivatable prodrug of doxazolidine targeting exosomes. J Med Chem 62: 1959-1970, 2019.
21. Kreger BT, Johansen ER, Cerione RA and Antonyak MA: The enrichment of survivin in exosomes from breast cancer cells treated with paclitaxel promotes cell survival and chemoresistance. Cancers 8: 111, 2016.
22. Melo SA, Luecke LB, Kahlert C, Fernandez AF, Gammon ST, Kaye J, LeBleu VS, Mittendorf EA, Weitz J, Rahbari N, *et al*: Glypican-1 identifies cancer exosomes and detects early pancreatic cancer. Nature 523: 177-182, 2015.
23. Zhao X, Wu D, Ma X, Wang J, Hou W and Zhang W: Exosomes as drug carriers for cancer therapy and challenges regarding exosome uptake. Biomed Pharmacother 128: 110237, 2020.
24. Zhou X, Yan Y, Shen Y, Xu M and Xu W: Exosomes: Emerging insights into the progression of pancreatic cancer. Int J Biol Sci 20: 4098-4113, 2024.
25. Qin C, Li T, Lin C, Zhao B, Li Z, Zhao Y and Wang W: The systematic role of pancreatic cancer exosomes: Distant communication, liquid biopsy and future therapy. Cancer Cell Int 24: 264, 2024.
26. Chen Y, Kleeff J and Sunami Y: Pancreatic cancer cell- and cancer-associated fibroblast-derived exosomes in disease progression, metastasis, and therapy. Discov Oncol 15: 253, 2024.
27. Zhou Y, Feng J, Wang Q, Zhao Y, Ding H, Jiang K, Ji H, Tang Z and Dai R: Knowledge mapping and research trends of exosomes in pancreatic cancer: A bibliometric analysis and review (2013-2023). Front Oncol 14: 1362436, 2024.
28. Trifylli EM, Kriebardis AG, Koustas E, Papadopoulos N, Fortis SP, Tzounakas VL, Anastasiadi AT, Sarantis P, Vasileiadi S, Tsagarakis A, *et al*: A current synopsis of the emerging role of extracellular vesicles and Micro-RNAs in pancreatic cancer: A Forward-Looking plan for diagnosis and treatment. Int J Mol Sci 25: 3406, 2024.
29. Sha G, Zhang W, Jiang Z, Zhao Q, Wang D and Tang D: Exosomal non-coding RNA: A new frontier in diagnosing and treating pancreatic cancer: A review. Int J Biol Macromol 263: 130149, 2024.
30. Papadakos SP, Dedes N, Pergaris A, Gazouli M and Theocharis S: Exosomes in the Treatment of Pancreatic Cancer: A moonshot to PDAC treatment? Int J Mol Sci 23: 3620, 2022.
31. Ariston Gabriel AN, Wang F, Jiao Q, Yvette U, Yang X, Al-Ameri SA, Du L, Wang YS and Wang C: The involvement of exosomes in the diagnosis and treatment of pancreatic cancer. Mol Cancer 19: 132, 2020.
32. Fang X, Lan H, Jin K and Qian J: Pancreatic cancer and exosomes: Role in progression, diagnosis, monitoring, and treatment. Front Oncol 13: 1149551, 2023.
33. Bunduc S, Gede N, Váncsa S, Lillik V, Kiss S, Juhász MF, Erőss B, Szakács Z, Gheorghe C, Mikó A and Hegyi P: Exosomes as prognostic biomarkers in pancreatic ductal adenocarcinoma-a systematic review and meta-analysis. Transl Res 244: 126-136, 2022.
34. Xu B, Chen Y, Peng M, Zheng JH and Zuo C: Exploring the potential of exosomes in diagnosis and drug delivery for pancreatic ductal adenocarcinoma. Int J Cancer 152: 110-122, 2023.
35. Hsu SK, Jadhao M, Liao WT, Chang WT, Lin IL and Chiu CC: The role of exosomes in pancreatic ductal adenocarcinoma progression and their potential as biomarkers. Cancers (Basel) 15: 1776, 2023.
36. Han L, Zhao Z, Yang K, Xin M, Zhou L, Chen S, Zhou S, Tang Z, Ji H and Dai R: Application of exosomes in the diagnosis and treatment of pancreatic diseases. Stem Cell Res Ther 13: 153, 2022.
37. Doyle LM and Wang MZ: Overview of extracellular vesicles, their origin, composition, purpose, and methods for exosome isolation and analysis. Cells 8: 727, 2019.
38. Wortzel I, Dror S, Kenific CM and Lyden D: Exosome-mediated metastasis: Communication from a distance. Dev Cell 49: 347-360, 2019.

39. He C, Zheng S, Luo Y and Wang B: Exosome theranostics: Biology and translational medicine. Theranostics 8: 237-255, 2018.
40. Duan SL, Fu WJ, Jiang YK, Peng LS, Ousmane D, Zhang ZJ and Wang JP: Emerging role of exosome-derived non-coding RNAs in tumor-associated angiogenesis of tumor microenvironment. Front Mol Biosci 10: 1220193, 2023.
41. Kalluri R and LeBleu VS: The biology, function, and biomedical applications of exosomes. Science 367: eaau6977, 2020.
42. Pegtel DM and Gould SJ: Exosomes. Annu Rev Biochem 88: 487-514, 2019.
43. Dai X, Ye Y and He F: Emerging innovations on exosome-based onco-therapeutics. Front Immunol 13: 865245, 2022.
44. Skotland T, Hessvik NP, Sandvig K and Llorente A: Exosomal lipid composition and the role of ether lipids and phosphoinositides in exosome biology. J Lipid Res 60: 9-18, 2019.
45. Mashouri L, Yousefi H, Aref AR, Ahadi AM, Molaei F and Alahari SK: Exosomes: Composition, biogenesis, and mechanisms in cancer metastasis and drug resistance. Mol Cancer 18: 75, 2019.
46. He C, Li L, Wang L, Meng W, Hao Y and Zhu G: Exosome-mediated cellular crosstalk within the tumor microenvironment upon irradiation. Cancer Biol Med 18: 21-33, 2021.
47. Peng H, Ji W, Zhao R, Yang J, Lu Z, Li Y and Zhang X: Exosome: A significant nano-scale drug delivery carrier. J Mater Chem B 8: 7591-7608, 2020.
48. Im H, Shao H, Weissleder R, Castro CM and Lee H: Nano-plasmonic exosome diagnostics. Expert Rev Mol Diagn 15: 725-733, 2015.
49. Hamzah RN, Alghazali KM, Biris AS and Griffin RJ: Exosome traceability and cell source dependence on composition and cell-cell cross talk. Int J Mol Sci 22: 5346, 2021.
50. Kawamura S, Iinuma H, Wada K, Takahashi K, Minezaki S, Kainuma M, Shibuya M, Miura F and Sano K: Exosome-encapsulated microRNA-4525, microRNA-451a and microRNA-21 in portal vein blood is a high-sensitive liquid biomarker for the selection of high-risk pancreatic ductal adenocarcinoma patients. J Hepatobiliary Pancreat Sci 26: 63-72, 2019.
51. Xu L, Wu LF and Deng FY: Exosome: An emerging source of biomarkers for human diseases. Curr Mol Med 19: 387-394, 2019.
52. Lobb RJ, Becker M, Wen SW, Wong CS, Wiegmans AP, Leimgruber A and Möller A: Optimized exosome isolation protocol for cell culture supernatant and human plasma. J Extracell Vesicles 4: 27031, 2015.
53. Tang YT, Huang YY, Zheng L, Qin SH, Xu XP, An TX, Xu Y, Wu YS, Hu XM, Ping BH and Wang Q: Comparison of isolation methods of exosomes and exosomal RNA from cell culture medium and serum. Int J Mol Med 40: 834-844, 2017.
54. Vaswani K, Mitchell MD, Holland OJ, Qin Koh Y, Hill RJ, Harb T, Davies PSW and Peiris H: A Method for the isolation of exosomes from human and bovine milk. J Nutr Metab 2019: 5764740, 2019.
55. Tayebi M, Zhou Y, Tripathi P, Chandramohanadas R and Ai Y: Exosome purification and analysis using a facile microfluidic hydrodynamic trapping device. Anal Chem 92: 10733-10742, 2020.
56. Gonzalez H, Hagerling C and Werb Z: Roles of the immune system in cancer: From tumor initiation to metastatic progression. Genes Dev 32: 1267-1284, 2018.
57. He Z, Wang J, Zhu C, Xu J, Chen P, Jiang X, Chen Y, Jiang J and Sun C: Exosome-derived FGD5-AS1 promotes tumor-associated macrophage M2 polarization-mediated pancreatic cancer cell proliferation and metastasis. Cancer Lett 548: 215751, 2022.
58. Zhang Y, Liu Y, Liu H and Tang WH: Exosomes: Biogenesis, biologic function and clinical potential. Cell Biosci 9: 19, 2019.
59. Wang S, Zheng Y, Yang F, Zhu L, Zhu XQ, Wang ZF, Wu XL, Zhou CH, Yan JY, Hu BY, *et al*: The molecular biology of pancreatic adenocarcinoma: Translational challenges and clinical perspectives. Signal Transduct Target Ther 6: 249, 2021.
60. Kumari N and Choi SH: Tumor-associated macrophages in cancer: Recent advancements in cancer nanoimmunotherapies. J Exp Clin Cancer Res 41: 68, 2022.
61. Qian Y, Yin Y, Zheng X, Liu Z and Wang X: Metabolic regulation of tumor-associated macrophage heterogeneity: Insights into the tumor microenvironment and immunotherapeutic opportunities. Biomark Res 12: 1, 2024.
62. Mao X, Xu J, Wang W, Liang C, Hua J, Liu J, Zhang B, Meng Q, Yu X and Shi S: Crosstalk between cancer-associated fibroblasts and immune cells in the tumor microenvironment: New findings and future perspectives. Mol Cancer 20: 131, 2021.
63. Pritchard A, Tousif S, Wang Y, Hough K, Khan S, Strenkowski J, Chacko BK, Darley-Usmar VM and Deshane JS: Lung tumor cell-derived exosomes promote M2 macrophage polarization. Cells 9: 1303, 2020.
64. Pan Y, Tang H, Li Q, Chen G and Li D: Exosomes and their roles in the chemoresistance of pancreatic cancer. Cancer Med 11: 4979-4988, 2022.
65. Papadakos SP, Machairas N, Stergiou IE, Arvanitakis K, Germanidis G, Frampton AE and Theocharis S: Unveiling the Yin-Yang balance of M1 and M2 macrophages in hepatocellular carcinoma: Role of exosomes in tumor microenvironment and immune modulation. Cells 12: 2036, 2023.
66. Wang L, Li Z, Shen J, Liu Z, Liang J, Wu X, Sun X and Wu Z: Exosome-like vesicles derived by *Schistosoma japonicum* adult worms mediates M1 type immune-activity of macrophage. Parasitol Res 114: 1865-1873, 2015.
67. Chehelgerdi M, Chehelgerdi M, Allela OQB, Pecho RDC, Jayasankar N, Rao DP, Thamaraikani T, Vasanthan M, Viktor P, Lakshmaiya N, *et al*: Progressing nanotechnology to improve targeted cancer treatment: Overcoming hurdles in its clinical implementation. Mol Cancer 22: 169, 2023.
68. Cui X, Fu Q, Wang X, Xia P, Cui X and Bai X, Lu Z: Molecular mechanisms and clinical applications of exosomes in prostate cancer. Biomark Res 10: 56, 2022.
69. Zhang J, Li S, Li L, Guo C, Yao J and Mi S: Exosome and exosomal microRNA: Trafficking, sorting, and function. Genomics Proteomics Bioinformatics 13: 17-24, 2015.
70. Milane L, Singh A, Mattheolabakis G, Suresh M and Amiji MM: Exosome mediated communication within the tumor microenvironment. J Control Release 219: 278-294, 2015.
71. Khan MI and Alsayed R: Exosome-mediated response to cancer therapy: Modulation of Epigenetic Machinery. Int J Mol Sci 23: 6222, 2022.
72. McAndrews KM, Xiao F, Chronopoulos A, LeBleu VS, Kugeratski FG and Kalluri R: Exosome-mediated delivery of CRISPR/Cas9 for targeting of oncogenic Kras(G12D) in pancreatic cancer. Life Sci Alliance 4: e202000875, 2021.
73. Su MJ, Aldawsari H and Amiji M: Pancreatic cancer cell exosome-mediated macrophage reprogramming and the role of MicroRNAs 155 and 125b2 transfection using nanoparticle delivery systems. Sci Rep 6: 30110, 2016.
74. Caruso Bavisotto C, Cappello F, Macario AJL, Conway de Macario E, Logozzi M, Fais S and Campanella C: Exosomal HSP60: A potentially useful biomarker for diagnosis, assessing prognosis, and monitoring response to treatment. Expert Rev Mol Diagn 17: 815-822, 2017.
75. Dudeja V, Mujumdar N, Phillips P, Chugh R, Borja-Cacho D, Dawra RK, Vickers SM and Saluja AK: Heat shock protein 70 inhibits apoptosis in cancer cells through simultaneous and independent mechanisms. Gastroenterology 136: 1772-1782, 2009.
76. Shaashua L, Ben-Shmuel A, Pevsner-Fischer M, Friedman G, Levi-Galibov O, Nandakumar S, Barki D, Nevo R, Brown LE, Zhang W, *et al*: BRCA mutational status shapes the stromal microenvironment of pancreatic cancer linking clusterin expression in cancer associated fibroblasts with HSF1 signaling. Nat Commun 13: 6513, 2022.
77. Jin H, Liu P, Wu Y, Meng X, Wu M, Han J and Tan X: Exosomal zinc transporter ZIP4 promotes cancer growth and is a novel diagnostic biomarker for pancreatic cancer. Cancer Sci 109: 2946-2956, 2018.
78. Castillo J, Bernard V, San Lucas FA, Allenson K, Capello M, Kim DU, Gascoyne P, Mulu FC, Stephens BM, Huang J, *et al*: Surfaceome profiling enables isolation of cancer-specific exosomal cargo in liquid biopsies from pancreatic cancer patients. Ann Oncol 29: 223-229, 2018.
79. Zhang R, Loganathan S, Humphreys I and Srivastava SK: Benzyl isothiocyanate-induced DNA damage causes G2/M cell cycle arrest and apoptosis in human pancreatic cancer cells. J Nutr 136: 2728-2734, 2006.
80. Ristorcelli E, Beraud E, Mathieu S, Lombardo D and Verine A: Essential role of Notch signaling in apoptosis of human pancreatic tumoral cells mediated by exosomal nanoparticles. Int J Cancer 125: 1016-1026, 2009.
81. Huang J, Chen P, Liu K, Liu J, Zhou B, Wu R, Peng Q, Liu ZX, Li C, Kroemer G, *et al*: CDK1/2/5 inhibition overcomes IFNG-mediated adaptive immune resistance in pancreatic cancer. Gut 70: 890-899, 2021.
82. Hayes TK, Neel NF, Hu C, Gautam P, Chenard M, Long B, Aziz M, Kassner M, Bryant KL, Pierobon M, *et al*: Long-term ERK inhibition in KRAS-mutant pancreatic cancer is associated with MYC degradation and Senescence-like growth suppression. Cancer Cell 29: 75-89, 2016.

83. Li B, Cao Y, Sun M and Feng H: Expression, regulation, and function of exosome-derived miRNAs in cancer progression and therapy. FASEB J 35: e21916, 2021.
84. Sun W, Ren Y, Lu Z and Zhao X: The potential roles of exosomes in pancreatic cancer initiation and metastasis. Mol Cancer 19: 135, 2020.
85. Zhou B, Xu JW, Cheng YG, Gao JY, Hu SY, Wang L and Zhan HX: Early detection of pancreatic cancer: Where are we now and where are we going? Int J Cancer 141: 231-241, 2017.
86. Zhao C, Gao F, Weng S and Liu Q: Pancreatic cancer and associated exosomes. Cancer Biomark 20: 357-367, 2017.
87. Yan Y, Fu G and Ming L: Role of exosomes in pancreatic cancer. Oncol Lett 15: 7479-7488, 2018.
88. Wang X, Luo G, Zhang K, Cao J, Huang C, Jiang T, Liu B, Su L and Qiu Z: Hypoxic tumor-derived exosomal miR-301a mediates M2 macrophage polarization via PTEN/PI3Kγ to promote pancreatic cancer metastasis. Cancer Res 78: 4586-4598, 2018.
89. Chiba M, Kubota S, Sato K and Monzen S: Exosomes released from pancreatic cancer cells enhance angiogenic activities via dynamin-dependent endocytosis in endothelial cells in vitro. Sci Rep 8: 11972, 2018.
90. Li J, Li Z, Jiang P, Peng M, Zhang X, Chen K, Liu H, Bi H, Liu X and Li X: Circular RNA IARS (circ-IARS) secreted by pancreatic cancer cells and located within exosomes regulates endothelial monolayer permeability to promote tumor metastasis. J Exp Clin Cancer Res 37: 177, 2018.
91. Zhou X, Zhong F, Yan Y, Wu S, Wang H, Liu J, Li F, Cui D and Xu M: Pancreatic cancer cell-derived exosomes promote lymphangiogenesis by downregulating ABHD11-AS1 expression. Cancers (Basel) 14: 4612, 2022.
92. Li M, Zhou J, Zhang Z, Li J, Wang F, Ma L, Tian X, Mao Z and Yang Y: Exosomal miR-485-3p derived from pancreatic ductal epithelial cells inhibits pancreatic cancer metastasis through targeting PAK1. Chin Med J 135: 2326-2337, 2022.
93. Di Pace AL, Pelosi A, Fiore PF, Tumino N, Besi F, Quatrini L, Santopolo S, Vacca P and Moretta L: MicroRNA analysis of Natural Killer cell-derived exosomes: The microRNA let-7b-5p is enriched in exosomes and participates in their anti-tumor effects against pancreatic cancer cells. Oncoimmunology 12: 2221081, 2023.
94. Sun H, Shi K, Qi K, Kong H, Zhang J, Dai S, Ye W, Deng T, He Q and Zhou M: Natural killer cell-derived exosomal miR-3607-3p inhibits pancreatic cancer progression by targeting IL-26. Front Immunol 10: 2819, 2019.
95. Yin Z, Zhou Y, Ma T, Chen S, Shi N, Zou Y, Hou B and Zhang C: Down-regulated lncRNA SBF2-AS1 in M2 macrophage-derived exosomes elevates miR-122-5p to restrict XIAP, thereby limiting pancreatic cancer development. J Cell Mol Med 24: 5028-5038, 2020.
96. Xie X, Ji J, Chen X, Xu W, Chen H, Zhu S, Wu J, Wu Y, Sun Y, Sai W, *et al*: Human umbilical cord mesenchymal stem cell-derived exosomes carrying hsa-miRNA-128-3p suppress pancreatic ductal cell carcinoma by inhibiting Galectin-3. Clin Transl Oncol 24: 517-531, 2022.
97. Torphy RJ, Fujiwara Y and Schulick RD: Pancreatic cancer treatment: Better, but a long way to go. Surg Today 50: 1117-1125, 2020.
98. Zhao Z and Liu W: Pancreatic cancer: A review of risk factors, diagnosis, and treatment. Technol Cancer Res Treat 19: 1533033820962117, 2020.
99. Cai J, Chen H, Lu M, Zhang Y, Lu B, You L, Zhang T, Dai M and Zhao Y: Advances in the epidemiology of pancreatic cancer: Trends, risk factors, screening, and prognosis. Cancer Lett 520: 1-11, 2021.
100. Loveday BPT, Lipton L and Thomson BN: Pancreatic cancer: An update on diagnosis and management. Aust J Gen Pract 48: 826-831, 2019.
101. Scarà S, Bottoni P and Scatena R: CA 19-9: Biochemical and clinical aspects. Adv Exp Med Biol 867: 247-260, 2015.
102. Nakamura K, Zhu Z, Roy S, Jun E, Han H, Munoz RM, Nishiwada S, Sharma G, Cridebring D, Zenhausern F, *et al*: An Exosome-based transcriptomic signature for noninvasive, early detection of patients with pancreatic ductal adenocarcinoma: A multicenter cohort study. Gastroenterology 163: 1252-1266.e2, 2022.
103. Tempero MA, Malafa MP, Al-Hawary M, Behrman SW, Benson AB, Cardin DB, Chiorean EG, Chung V, Czito B, Del Chiaro M, *et al*: Pancreatic adenocarcinoma, version 2.2021, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 19: 439-457, 2021.
104. Vincent A, Herman J, Schulick R, Hruban RH and Goggins M: Pancreatic cancer. Lancet 378: 607-620, 2011.
105. Hu ZI and O'Reilly EM: Therapeutic developments in pancreatic cancer. Nat Rev Gastroenterol Hepatol 21: 7-24, 2024.
106. Lupo F, Pezzini F, Pasini D, Fiorini E, Adamo A, Veghini L, Bevere M, Frusteri C, Delfino P, D'agosto S, *et al*: Axon guidance cue SEMA3A promotes the aggressive phenotype of basal-like PDAC. Gut 73: 1321-1335, 2024.
107. Reese M and Dhayat SA: Small extracellular vesicle non-coding RNAs in pancreatic cancer: molecular mechanisms and clinical implications. J Hematol Oncol 14: 141, 2021.
108. Ran Z, Wu S, Ma Z, Chen X, Liu J and Yang J: Advances in exosome biomarkers for cervical cancer. Cancer Med 11: 4966-4978, 2022.
109. Yuan Y, Li H, Pu W, Chen L, Guo D, Jiang H, He B, Qin S, Wang K, Li N, *et al*: Cancer metabolism and tumor microenvironment: Fostering each other? Sci China Life Sci 65: 236-279, 2022.
110. Wu L, Zhou WB, Zhou J, Wei Y, Wang HM, Liu XD, Chen XC, Wang W, Ye L, Yao LC, *et al*: Circulating exosomal microRNAs as novel potential detection biomarkers in pancreatic cancer. Oncol Lett 20: 1432-1440, 2020.
111. Condrat CE, Thompson DC, Barbu MG, Bugnar OL, Boboc A, Cretoiu D, Suciu N, Cretoiu SM and Voinea SC: miRNAs as biomarkers in disease: Latest findings regarding their role in diagnosis and prognosis. Cells 9: 276, 2020.
112. Ouyang H, Gore J, Deitz S and Korc M: microRNA-10b enhances pancreatic cancer cell invasion by suppressing TIP30 expression and promoting EGF and TGF-β actions. Oncogene 33: 4664-4674, 2014.
113. Yu D, Li Y, Wang M, Gu J, Xu W, Cai H, Fang X and Zhang X: Exosomes as a new frontier of cancer liquid biopsy. Mol Cancer 21: 56, 2022.
114. He C, Li L, Wang L, Meng W, Hao Y and Zhu G: Exosome-mediated cellular crosstalk within the tumor microenvironment upon irradiation. Cancer Biol Med 18: 21-33, 2021.
115. Jiang Z, Wang H, Mou Y, Li L and Jin W: Functions and clinical applications of exosomes in pancreatic cancer. Mol Biol Rep 49: 11037-11048, 2022.
116. Ashrafizadeh M, Rabiee N, Kumar AP, Sethi G, Zarrabi A and Wang Y: Long noncoding RNAs (lncRNAs) in pancreatic cancer progression. Drug Discov Today 27: 2181-2198, 2022.
117. Kato S and Honda K: Use of biomarkers and imaging for early detection of pancreatic cancer. Cancers (Basel) 12: 1965, 2020.
118. Zhao X, Ren Y and Lu Z: Potential diagnostic and therapeutic roles of exosomes in pancreatic cancer. Biochim Biophys Acta Rev Cancer 1874: 188414, 2020.
119. Frampton AE, Prado MM, López-Jiménez E, Fajardo-Puerta AB, Jawad ZAR, Lawton P, Giovannetti E, Habib NA, Castellano L, Stebbing J, *et al*: Glypican-1 is enriched in circulating-exosomes in pancreatic cancer and correlates with tumor burden. Oncotarget 9: 19006-19013, 2018.
120. Marin AM, Mattar SB, Amatuzzi RF, Chammas R, Uno M, Zanette DL and Aoki MN: Plasma exosome-derived microRNAs as potential diagnostic and prognostic biomarkers in brazilian pancreatic cancer patients. Biomolecules 12: 769, 2022.
121. Wang L, Wu J, Ye N, Li F, Zhan H, Chen S and Xu J: Plasma-derived exosome MiR-19b acts as a diagnostic marker for pancreatic cancer. Front Oncol 11: 739111, 2021.
122. Nakamura S, Sadakari Y, Ohtsuka T, Okayama T, Nakashima Y, Gotoh Y, Saeki K, Mori Y, Nakata K, Miyasaka Y, *et al*: Pancreatic Juice exosomal MicroRNAs as biomarkers for detection of pancreatic ductal adenocarcinoma. Ann Surg Oncol 26: 2104-2111, 2019.
123. Chen SL, Ma M, Yan L, Xiong SH, Liu Z, Li S, Liu T, Shang S, Zhang YY, Zeng H, *et al*: Clinical significance of exosomal miR-1231 in pancreatic cancer]. Zhonghua Zhong Liu Za Zhi 41: 46-49, 2019 (In Chinese).
124. Corrigendum to Serum exosomal miR-451a acts as a candidate marker for pancreatic cancer. Int J Biol Markers 37: 224, 2022.
125. Yu S, Li Y, Liao Z, Wang Z, Wang Z, Li Y, Qian L, Zhao J, Zong H, Kang B, *et al*: Plasma extracellular vesicle long RNA profiling identifies a diagnostic signature for the detection of pancreatic ductal adenocarcinoma. Gut 69: 540-550, 2020.
126. Hong L, Xu L, Jin L, Xu K, Tang W, Zhu Y, Qiu X and Wang J: Exosomal circular RNA hsa_circ_0006220, and hsa_circ_0001666 as biomarkers in the diagnosis of pancreatic cancer. J Clin Lab Anal 36: e24447, 2022.

127. Yadav DK, Bai X, Yadav RK, Singh A, Li G, Ma T, Chen W and Liang T: Liquid biopsy in pancreatic cancer: The beginning of a new era. Oncotarget 9: 26900-26933, 2018.
128. Allenson K, Castillo J, San Lucas FA, Scelo G, Kim DU, Bernard V, Davis G, Kumar T, Katz M, Overman MJ, *et al*: High prevalence of mutant KRAS in circulating exosome-derived DNA from early-stage pancreatic cancer patients. Ann Oncol 28: 741-747, 2017.
129. Mizukami K, Iwasaki Y, Kawakami E, Hirata M, Kamatani Y, Matsuda K, Endo M, Sugano K, Yoshida T, Murakami Y, *et al*: Genetic characterization of pancreatic cancer patients and prediction of carrier status of germline pathogenic variants in cancer-predisposing genes. EBioMedicine 60: 103033, 2020.
130. Lai E, Ziranu P, Spanu D, Dubois M, Pretta A, Tolu S, Camera S, Liscia N, Mariani S, Persano M, *et al*: BRCA-mutant pancreatic ductal adenocarcinoma. Br J Cancer 125: 1321-1332, 2021.
131. Moutinho-Ribeiro P, Adem B, Batista I, Silva M, Silva S, Ruivo CF, Morais R, Peixoto A, Coelho R, Costa-Moreira P, *et al*: Exosomal glypican-1 discriminates pancreatic ductal adenocarcinoma from chronic pancreatitis. Dig Liver Dis 54: 871-877, 2022.
132. Yoshizawa N, Sugimoto K, Tameda M, Inagaki Y, Ikejiri M, Inoue H, Usui M, Ito M and Takei Y: miR-3940-5p/miR-8069 ratio in urine exosomes is a novel diagnostic biomarker for pancreatic ductal adenocarcinoma. Oncol Lett 19: 2677-2684, 2020.
133. Xie Z, Gao Y, Ho C, Li L, Jin C, Wang X, Zou C, Mao Y, Wang X, Li Q, *et al*: Exosome-delivered CD44v6/C1QBP complex drives pancreatic cancer liver metastasis by promoting fibrotic liver microenvironment. Gut 71: 568-579, 2022.
134. Ishihara M, Kageyama S, Miyahara Y, Ishikawa T, Ueda S, Soga N, Naota H, Mukai K, Harada N, Ikeda H and Shiku H: MAGE-A4, NY-ESO-1 and SAGE mRNA expression rates and co-expression relationships in solid tumours. BMC Cancer 20: 606, 2020.
135. Hashimoto K, Nishimura S, Ito T and Akagi M: Clinicopathological assessment of cancer/testis antigens NY-ESO-1 and MAGE-A4 in highly aggressive soft tissue sarcomas. Diagnostics (Basel) 12: 733, 2022.
136. Wu H, Chen X, Ji J, Zhou R, Liu J, Ni W, Qu L, Ni H, Ni R, Bao B and Xiao M: Progress of exosomes in the diagnosis and treatment of pancreatic cancer. Gene Test Mol Biomarkers 23: 215-222, 2019.
137. Xu M, Hu W, Liu Z, Xia J, Chen S, Wang PG and Yang S: Glycoproteomic bioanalysis of exosomes by LC-MS for early diagnosis of pancreatic cancer. Bioanalysis 13: 861-864, 2021.
138. Zhao Y, Tang J, Jiang K, Liu SY, Aicher A and Heeschen C: Liquid biopsy in pancreatic cancer-Current perspective and future outlook. Biochim Biophys Acta Rev Cancer 1878: 188868, 2023.
139. Raufi AG, May MS, Hadfield MJ, Seyhan AA and El-Deiry WS: Advances in Liquid Biopsy Technology and Implications for Pancreatic Cancer. Int J Mol Sci 24: 4238, 2023.
140. Haeberle L, Schramm M, Goering W, Frohn L, Driescher C, Hartwig W, Preissinger-Heinzel HK, Beyna T, Neuhaus H, Fuchs K, *et al*: Molecular analysis of cyst fluids improves the diagnostic accuracy of pre-operative assessment of pancreatic cystic lesions. Sci Rep 11: 2901, 2021.
141. Karunakaran M and Barreto SG: Surgery for pancreatic cancer: Current controversies and challenges. Future Oncol 17: 5135-5162, 2021.
142. Strobel O and Neoptolemos J: Optimizing the outcomes of pancreatic cancer surgery. Nat Rev Clin Oncol 16: 11-26, 2019.
143. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, Seay T, Tjulandin SA, Ma WW, Saleh MN, *et al*: Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 369: 1691-1703, 2013.
144. Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardière C, *et al*: FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 364: 1817-1825, 2011.
145. Yoshida K, Iwashita T, Uemura S, Maruta A, Okuno M, Ando N, Iwata K, Kawaguchi J, Mukai T and Shimizu M: A multicenter prospective phase II study of first-line modified FOLFIRINOX for unresectable advanced pancreatic cancer. Oncotarget 8: 111346-111355, 2017.
146. Pajewska M, Partyka O, Czerw A, Deptała A, Cipora E, Gąska I, Wojtaszek M, Sygit K, Sygit M, Krzych-Fałta E, *et al*: Management of metastatic pancreatic Cancer-comparison of global guidelines over the last 5 years. Cancers (Basel) 15: 4400, 2023.
147. Strickler JH, Satake H, George TJ, Yaeger R, Hollebecque A, Garrido-Laguna I, Schuler M, Burns TF, Coveler AL, Falchook GS, *et al*: Sotorasib in KRAS p.G12C-mutated advanced pancreatic cancer. N Engl J Med 388: 33-43, 2023.
148. Golan T, Hammel P, Reni M, Van Cutsem E, Macarulla T, Hall MJ, Park JO, Hochhauser D, Arnold D, Oh DY, *et al*: Maintenance Olaparib for Germline BRCA-mutated metastatic pancreatic cancer. N Engl J Med 381: 317-327, 2019.
149. Ijichi H, Chytil A, Gorska AE, Aakre ME, Fujitani Y, Fujitani S, Wright CV and Moses HL: Aggressive pancreatic ductal adenocarcinoma in mice caused by pancreas-specific blockade of transforming growth factor-beta signaling in cooperation with active Kras expression. Genes Dev 20: 3147-3160, 2006.
150. Wang Z, Ali S, Banerjee S, Bao B, Li Y, Azmi AS, Korc M and Sarkar FH: Activated K-Ras and INK4a/Arf deficiency promote aggressiveness of pancreatic cancer by induction of EMT consistent with cancer stem cell phenotype. J Cell Physiol 228: 556-562, 2013.
151. Pirlog R and Calin GA: KRAS mutations as essential promoters of lymphangiogenesis via extracellular vesicles in pancreatic cancer. J Clin Invest 132: e161454, 2022.
152. Chang WH, Nguyen TT, Hsu CH, Bryant KL, Kim HJ, Ying H, Erickson JW, Der CJ, Cerione RA and Antonyak MA: KRAS-dependent cancer cells promote survival by producing exosomes enriched in Survivin. Cancer Lett 517: 66-77, 2021.
153. Wang-Gillam A, Li CP, Bodoky G, Dean A, Shan YS, Jameson G, Macarulla T, Lee KH, Cunningham D, Blanc JF, *et al*: Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): A global, randomised, open-label, phase 3 trial. Lancet 387: 545-557, 2016.
154. Ahmad SA, Duong M, Sohal DPS, Gandhi NS, Beg MS, Wang-Gillam A, Wade JL III, Chiorean EG, Guthrie KA, Lowy AM, *et al*: Surgical outcome results from SWOG S1505: A randomized clinical trial of mFOLFIRINOX versus Gemcitabine/Nab-paclitaxel for perioperative treatment of resectable pancreatic ductal adenocarcinoma. Ann Surg 272: 481-486, 2020.
155. Kunzmann V, Siveke JT, Algül H, Goekkurt E, Siegler G, Martens U, Waldschmidt D, Pelzer U, Fuchs M, Kullmann F, *et al*: Nab-paclitaxel plus gemcitabine versus nab-paclitaxel plus gemcitabine followed by FOLFIRINOX induction chemotherapy in locally advanced pancreatic cancer (NEOLAP-AIO-PAK-0113): A multicentre, randomised, phase 2 trial. Lancet Gastroenterol Hepatol 6: 128-138, 2021.
156. Pitt JM, André F, Amigorena S, Soria JC, Eggermont A, Kroemer G and Zitvogel L: Dendritic cell-derived exosomes for cancer therapy. J Clin Invest 126: 1224-1232, 2016.
157. Veerman RE, Güçlüler Akpinar G, Eldh M and Gabrielsson S: Immune Cell-derived extracellular vesicles-functions and therapeutic applications. Trends Mol Med 25: 382-394, 2019.
158. Zhao Y, Liu T and Zhou M: Immune-cell-derived exosomes for cancer therapy. Mol Pharm 19: 3042-3056, 2022.
159. Zhao LX, Zhang K, Shen BB and Li JN: Mesenchymal stem cell-derived exosomes for gastrointestinal cancer. World J Gastrointest Oncol 13: 1981-1996, 2021.
160. Zhou Y, Zhou W, Chen X, Wang Q, Li C, Chen Q, Zhang Y, Lu Y, Ding X and Jiang C: Bone marrow mesenchymal stem cells-derived exosomes for penetrating and targeted chemotherapy of pancreatic cancer. Acta Pharma Sin B 10: 1563-1575, 2020.
161. Zhang L, Xiang J, Zhang F, Liu L and Hu C: MSCs can be a double-edged sword in tumorigenesis. Front Oncol 12: 1047907, 2022.
162. Whiteside TL: Exosome and mesenchymal stem cell cross-talk in the tumor microenvironment. Semin Immunol 35: 69-79, 2018.
163. Ha DH, Kim HK, Lee J, Kwon HH, Park GH, Yang SH, Jung JY, Choi H, Lee JH, Sung S, *et al*: Mesenchymal Stem/stromal Cell-derived exosomes for immunomodulatory therapeutics and skin regeneration. Cells 9: 1157, 2020.
164. Fang S, Xu C, Zhang Y, Xue C, Yang C, Bi H, Qian X, Wu M, Ji K, Zhao Y, *et al*: Umbilical Cord-derived mesenchymal stem cell-derived exosomal MicroRNAs suppress myofibroblast differentiation by inhibiting the transforming growth factor-β/SMAD2 pathway during wound healing. Stem Cells Transl Med 5: 1425-1439, 2016.
165. Zhang Y, Hao Z, Wang P, Xia Y, Wu J, Xia D, Fang S and Xu S: Exosomes from human umbilical cord mesenchymal stem cells enhance fracture healing through HIF-1α-mediated promotion of angiogenesis in a rat model of stabilized fracture. Cell Prolif 52: e12570, 2019.

166. Eldaly AS, Mashaly SM, Fouda E, Emam OS, Aglan A, Abuasbeh J, Khurana A, Hamdar H and Fath AR: Systemic anti-inflammatory effects of mesenchymal stem cells in burn: A systematic review of animal studies. J Clin Transl Res 8: 276-291, 2022.
167. Xu X, Yin F, Guo M, Gan G, Lin G, Wen C, Wang J, Song P, Wang J, Qi ZQ and Zhong CQ: Quantitative proteomic analysis of exosomes from umbilical cord mesenchymal stem cells and rat bone marrow stem cells. Proteomics 23: e2200204, 2023.
168. Liu M, Yang Y, Zhao B, Yang Y, Wang J, Shen K, Yang X, Hu D, Zheng G and Han J: Exosomes derived from Adipose-derived mesenchymal stem cells ameliorate Radiation-induced brain injury by activating the SIRT1 pathway. Front Cell Dev Biol 9: 693782, 2021.
169. Shenoda BB and Ajit SK: Modulation of immune responses by exosomes derived from Antigen-presenting cells. Clin Med Insights Pathol 9 (Suppl 1): S1-S8, 2016.
170. Zaidi N, Soban M, Chen F, Kinkead H, Mathew J, Yarchoan M, Armstrong TD, Haider S and Jaffee EM: Role of in silico structural modeling in predicting immunogenic neoepitopes for cancer vaccine development. JCI Insight 5: e136991, 2020.
171. Yadav SS and Narayan G: Role of ROBO4 signalling in developmental and pathological angiogenesis. Biomed Res Int 2014: 683025, 2014.
172. Xu Y, Li WL, Fu L, Gu F and Ma YJ: Slit2/Robo1 signaling in glioma migration and invasion. Neurosci Bull 26: 474-478, 2010.
173. Wang L, Yang L, Zhuang T and Shi X: Tumor-derived exosomal miR-29b reduces angiogenesis in pancreatic cancer by silencing ROBO1 and SRGAP2. J Immunol Res 2022: 4769385, 2022.
174. Sun X, Zhang Y, Li B and Yang H: MTA1 promotes the invasion and migration of pancreatic cancer cells potentially through the HIF-α/VEGF pathway. J Recept Signal Transduct Res 38: 352-358, 2018.
175. Lee JK, Park SR, Jung BK, Jeon YK, Lee YS, Kim MK, Kim YG, Jang JY and Kim CW: Exosomes derived from mesenchymal stem cells suppress angiogenesis by down-regulating VEGF expression in breast cancer cells. PLoS One 8: e84256, 2013.
176. Pakravan K, Babashah S, Sadeghizadeh M, Mowla SJ, Mossahebi-Mohammadi M, Ataei F, Dana N and Javan M: MicroRNA-100 shuttled by mesenchymal stem cell-derived exosomes suppresses in vitro angiogenesis through modulating the mTOR/HIF-1α/VEGF signaling axis in breast cancer cells. Cell Oncol (Dordr) 40: 457-470, 2017.
177. Yang E, Wang X, Gong Z, Yu M, Wu H and Zhang D: Exosome-mediated metabolic reprogramming: The emerging role in tumor microenvironment remodeling and its influence on cancer progression. Signal Transduct Target Ther 5: 242, 2020.
178. Ye M, Huang X, Wu Q and Liu F: Senescent stromal cells in the tumor microenvironment: Victims or accomplices? Cancers (Basel) 15: 1927, 2023.
179. Zhao Y, Shen M, Wu L, Yang H, Yao Y, Yang Q, Du J, Liu L, Li Y and Bai Y: Stromal cells in the tumor microenvironment: Accomplices of tumor progression? Cell Death Dis 14: 587, 2023.
180. Dai X, Xie Y and Dong M: Cancer-associated fibroblasts derived extracellular vesicles promote angiogenesis of colorectal adenocarcinoma cells through miR-135b-5p/FOXO1 axis. Cancer Biol Ther 23: 76-88, 2022.
181. Qin Y, Liu X, Pan L, Zhou R and Zhang X: Long noncoding RNA MIR155HG facilitates pancreatic cancer progression through negative regulation of miR-802. J Cell Biochem 120: 17926-17934, 2019.
182. Ren Y, Jia HH, Xu YQ, Zhou X, Zhao XH, Wang YF, Song X, Zhu ZY, Sun T, Dou Y, *et al*: Paracrine and epigenetic control of CAF-induced metastasis: The role of HOTAIR stimulated by TGF-ß1 secretion. Mol Cancer 17: 5, 2018.
183. Sansone P, Savini C, Kurelac I, Chang Q, Amato LB, Strillacci A, Stepanova A, Iommarini L, Mastroleo C, Daly L, *et al*: Packaging and transfer of mitochondrial DNA via exosomes regulate escape from dormancy in hormonal therapy-resistant breast cancer. Proc Natl Acad Sci USA 114: E9066-E9075, 2017.
184. Achreja A, Zhao H, Yang L, Yun TH, Marini J and Nagrath D: Exo-MFA-A 13C metabolic flux analysis framework to dissect tumor microenvironment-secreted exosome contributions towards cancer cell metabolism. Metab Eng 43: 156-172, 2017.
185. Boelens MC, Wu TJ, Nabet BY, Xu B, Qiu Y, Yoon T, Azzam DJ, Twyman-Saint Victor C, Wiemann BZ, Ishwaran H, *et al*: Exosome transfer from stromal to breast cancer cells regulates therapy resistance pathways. Cell 159: 499-513, 2014.
186. Duong MN, Geneste A, Fallone F, Li X, Dumontet C and Muller C: The fat and the bad: Mature adipocytes, key actors in tumor progression and resistance. Oncotarget 8: 57622-57641, 2017.
187. Frisbie L, Buckanovich RJ and Coffman L: Carcinoma-associated mesenchymal stem/stromal cells: Architects of the pro-tumorigenic tumor microenvironment. Stem Cells 40: 705-715, 2022.
188. Habanjar O, Diab-Assaf M, Caldefie-Chezet F and Delort L: The impact of obesity, adipose tissue, and tumor microenvironment on macrophage polarization and metastasis. Biology (Basel) 11: 339, 2022.
189. Li B, Liu S, Yang Q, Li Z, Li J, Wu J, Sun S, Xu Z, Sun S and Wu Q: Macrophages in tumor-associated adipose microenvironment accelerate tumor progression. Adv Biol (Weinh) 7: e2200161, 2023.
190. Wen D, Liang T, Chen G, Li H, Wang Z, Wang J, Fu R, Han X, Ci T, Zhang Y, *et al*: Adipocytes encapsulating telratolimod recruit and polarize Tumor-Associated macrophages for cancer immunotherapy. Adv Sci (Weinh) 10: e2206001, 2023.
191. Masuda T, Fukuda A, Yamakawa G, Omatsu M, Namikawa M, Sono M, Fukunaga Y, Nagao M, Araki O, Yoshikawa T, *et al*: Pancreatic RECK inactivation promotes cancer formation, epithelial-mesenchymal transition, and metastasis. J Clin Invest 133: e161847, 2023.
192. Träger MM and Dhayat SA: Epigenetics of epithelial-to-mesenchymal transition in pancreatic carcinoma. Int J Cancer 141: 24-32, 2017.
193. Iwamoto C, Ohuchida K, Shinkawa T, Okuda S, Otsubo Y, Okumura T, Sagara A, Koikawa K, Ando Y, Shindo K, *et al*: Bone marrow-derived macrophages converted into cancer-associated fibroblast-like cells promote pancreatic cancer progression. Cancer Lett 512: 15-27, 2021.
194. Padoan A, Plebani M and Basso D: Inflammation and pancreatic cancer: Focus on metabolism, cytokines, and immunity. Int J Mol Sci 20: 676, 2019.
195. Malinova A, Veghini L, Real FX and Corbo V: Cell lineage infidelity in PDAC progression and therapy resistance. Front Cell Dev Biol 9: 795251, 2021.
196. Chou CW, Huang YK, Kuo TT, Liu JP and Sher YP: An overview of ADAM9: Structure, Activation, and regulation in human diseases. Int J Mol Sci 21: 7790, 2020.
197. Shang S, Wang J, Chen S, Tian R, Zeng H, Wang L, Xia M, Zhu H and Zuo C: Exosomal miRNA-1231 derived from bone marrow mesenchymal stem cells inhibits the activity of pancreatic cancer. Cancer Med 8: 7728-7740, 2019.
198. Yao X, Mao Y, Wu D, Zhu Y, Lu J, Huang Y, Guo Y, Wang Z, Zhu S, Li X and Lu Y: Exosomal circ_0030167 derived from BM-MSCs inhibits the invasion, migration, proliferation and stemness of pancreatic cancer cells by sponging miR-338-5p and targeting the Wif1/Wnt8/β-catenin axis. Cancer Lett 512: 38-50, 2021.
199. Ji R, Zhang B, Zhang X, Xue J, Yuan X, Yan Y, Wang M, Zhu W, Qian H, Xu W, *et al*: Exosomes derived from human mesenchymal stem cells confer drug resistance in gastric cancer. Cell Cycle 14: 2473-2483, 2015.
200. Gomis RR and Gawrzak S: Tumor cell dormancy. Mol Oncol 11: 62-78, 2017.
201. Haider MT, Smit DJ and Taipaleenmäki H: The Endosteal niche in breast cancer bone metastasis. Front Oncol 10: 335, 2020.
202. Ono M, Kosaka N, Tominaga N, Yoshioka Y, Takeshita F, Takahashi RU, Yoshida M, Tsuda H, Tamura K and Ochiya T: Exosomes from bone marrow mesenchymal stem cells contain a microRNA that promotes dormancy in metastatic breast cancer cells. Sci Signal 7: ra63, 2014.
203. Yang Y, Bucan V, Baehre H, von der Ohe J, Otte A and Hass R: Acquisition of new tumor cell properties by MSC-derived exosomes. Int J Oncol 47: 244-252, 2015.
204. Fu R, Shao Q, Yang B, Chen Y, Ye Q, Chen X and Zhu J: MiR-520a-5p/PPP5C regulation pattern is identified as the key to gemcitabine resistance in pancreatic cancer. Front Oncol 12: 903484, 2022.
205. Fan J, Wei Q, Koay EJ, Liu Y, Ning B, Bernard PW, Zhang N, Han H, Katz MH, Zhao Z and Hu Y: Chemoresistance transmission via exosome-Mediated EphA2 transfer in pancreatic cancer. Theranostics 8: 5986-5994, 2018.
206. Huang L, Rong Y, Tang X, Yi K, Qi P, Hou J, Liu W, He Y, Gao X, Yuan C and Wang F: Engineered exosomes as an in situ DC-primed vaccine to boost antitumor immunity in breast cancer. Mol Cancer 21: 45, 2022.

207. Tang W, Xia M, Liao Y, Fang Y, Wen G and Zhong J: Exosomes in triple negative breast cancer: From bench to bedside. Cancer Lett 527: 1-9, 2022.
208. Scavo MP, Depalo N, Tutino V, De Nunzio V, Ingrosso C, Rizzi F, Notarnicola M, Curri ML and Giannelli G: Exosomes for diagnosis and therapy in gastrointestinal cancers. Int J Mol Sci 21: 367, 2020.
209. Agrawal AK, Aqil F, Jeyabalan J, Spencer WA, Beck J, Gachuki BW, Alhakeem SS, Oben K, Munagala R, Bondada S and Gupta RC: Milk-derived exosomes for oral delivery of paclitaxel. Nanomedicine 13: 1627-1636, 2017.
210. Lux A, Kahlert C, Grützmann R and Pilarsky C: c-Met and PD-L1 on circulating exosomes as diagnostic and prognostic markers for pancreatic cancer. Int J Mol Sci 20: 3305, 2019.
211. Sakaue T, Koga H, Iwamoto H, Nakamura T, Ikezono Y, Abe M, Wada F, Masuda A, Tanaka T, Fukahori M, *et al*: Glycosylation of ascites-derived exosomal CD133: A potential prognostic biomarker in patients with advanced pancreatic cancer. Med Mol Morphol 52: 198-208, 2019.
212. Takahasi K, Iinuma H, Wada K, Minezaki S, Kawamura S, Kainuma M, Ikeda Y, Shibuya M, Miura F and Sano K: Usefulness of exosome-encapsulated microRNA-451a as a minimally invasive biomarker for prediction of recurrence and prognosis in pancreatic ductal adenocarcinoma. J Hepatobiliary Pancreat Sci 25: 155-161, 2018.
213. Wei Q, Li Z, Feng H and Ren L: Serum exosomal EphA2 is a prognostic biomarker in patients with pancreatic cancer. Cancer Manag Res 13: 3675-3683, 2021.
214. Chen D, Wu X, Xia M, Wu F, Ding J, Jiao Y, Zhan Q and An F: Upregulated exosomic miR-23b-3p plays regulatory roles in the progression of pancreatic cancer. Oncol Rep 38: 2182-2188, 2017.
215. Li Z, Tao Y, Wang X, Jiang P, Li J, Peng M, Zhang X, Chen K, Liu H, Zhen P, *et al*: Tumor-secreted exosomal miR-222 promotes tumor progression via regulating P27 expression and Re-localization in pancreatic cancer. Cell Physiol Biochem 51: 610-629, 2018.
216. Fang Y, Zhou W, Rong Y, Kuang T, Xu X, Wu W, Wang D and Lou W: Exosomal miRNA-106b from cancer-associated fibroblast promotes gemcitabine resistance in pancreatic cancer. Exp Cell Res 383: 111543, 2019.
217. Richards KE, Zeleniak AE, Fishel ML, Wu J, Littlepage LE and Hill R: Cancer-associated fibroblast exosomes regulate survival and proliferation of pancreatic cancer cells. Oncogene 36: 1770-1778, 2017.
218. Mikamori M, Yamada D, Eguchi H, Hasegawa S, Kishimoto T, Tomimaru Y, Asaoka T, Noda T, Wada H, Kawamoto K, *et al*: MicroRNA-155 controls exosome synthesis and promotes gemcitabine resistance in pancreatic ductal adenocarcinoma. Sci Rep 7: 42339, 2017.
219. Batista IA and Melo SA: Exosomes and the future of immunotherapy in pancreatic cancer. Int J Mol Sci 20: 567, 2019.
220. Yin Z, Ma T, Huang B, Lin L, Zhou Y, Yan J, Zou Y and Chen S: Macrophage-derived exosomal microRNA-501-3p promotes progression of pancreatic ductal adenocarcinoma through the TGFBR3-mediated TGF-β signaling pathway. J Exp Clin Cancer Res 38: 310, 2019.
221. Zhou W, Zhou Y, Chen X, Ning T, Chen H, Guo Q, Zhang Y, Liu P, Zhang Y, Li C, *et al*: Pancreatic cancer-targeting exosomes for enhancing immunotherapy and reprogramming tumor microenvironment. Biomaterials 268: 120546, 2021.
222. Li YJ, Wu JY, Wang JM, Hu XB, Cai JX and Xiang DX: Gemcitabine loaded autologous exosomes for effective and safe chemotherapy of pancreatic cancer. Acta Biomater 101: 519-530, 2020.
223. Kamerkar S, LeBleu VS, Sugimoto H, Yang S, Ruivo CF, Melo SA, Lee JJ and Kalluri R: Exosomes facilitate therapeutic targeting of oncogenic KRAS in pancreatic cancer. Nature 546: 498-503, 2017.
224. Xiao L, Erb U, Zhao K, Hackert T and Zöller M: Efficacy of vaccination with tumor-exosome loaded dendritic cells combined with cytotoxic drug treatment in pancreatic cancer. Oncoimmunology 6: e1319044, 2017.
225. Jang Y, Kim H, Yoon S, Lee H, Hwang J, Jung J, Chang JH, Choi J and Kim H: Exosome-based photoacoustic imaging guided photodynamic and immunotherapy for the treatment of pancreatic cancer. J Control Release 330: 293-304, 2021.
226. Que RS, Lin C, Ding GP, Wu ZR and Cao LP: Increasing the immune activity of exosomes: The effect of miRNA-depleted exosome proteins on activating dendritic cell/cytokine-induced killer cells against pancreatic cancer. J Zhejiang Univ Sci B 17: 352-360, 2016.
227. Duan L, Xu L, Xu X, Qin Z, Zhou X, Xiao Y, Liang Y and Xia J: Exosome-mediated delivery of gene vectors for gene therapy. Nanoscale 13: 1387-1397, 2021.
228. Moon B and Chang S: Exosome as a delivery vehicle for cancer therapy. Cells 11: 316, 2022.
229. Arrighetti N, Corbo C, Evangelopoulos M, Pastò A, Zuco V and Tasciotti E: Exosome-like nanovectors for drug delivery in cancer. Curr Med Chem 26: 6132-6148, 2019.
230. Liang Y, Duan L, Lu J and Xia J: Engineering exosomes for targeted drug delivery. Theranostics 11: 3183-3195, 2021.
231. Guimarães D, Cavaco-Paulo A and Nogueira E: Design of liposomes as drug delivery system for therapeutic applications. Int J Pharm 601: 120571, 2021.
232. Lamichhane TN, Jeyaram A, Patel DB, Parajuli B, Livingston NK, Arumugasaamy N, Schardt JS and Jay SM: Oncogene knockdown via active loading of small RNAs into extracellular vesicles by sonication. Cell Mol Bioeng 9: 315-324, 2016.
233. Zuo L, Tao H, Xu H, Li C, Qiao G, Guo M, Cao S, Liu M and Lin X: Exosomes-coated miR-34a displays potent antitumor activity in pancreatic cancer both in vitro and in vivo. Drug Des Devel Ther 14: 3495-3507, 2020.
234. Ding Y, Cao F, Sun H, Wang Y, Liu S, Wu Y, Cui Q, Mei W and Li F: Exosomes derived from human umbilical cord mesenchymal stromal cells deliver exogenous miR-145-5p to inhibit pancreatic ductal adenocarcinoma progression. Cancer Lett 442: 351-361, 2019.
235. Duan H, Liu Y, Gao Z and Huang W: Recent advances in drug delivery systems for targeting cancer stem cells. Acta Pharm Sin B 11: 55-70, 2021.
236. Guo G, Tan Z, Liu Y, Shi F and She J: The therapeutic potential of stem cell-derived exosomes in the ulcerative colitis and colorectal cancer. Stem Cell Res Ther 13: 138, 2022.
237. Pascucci L, Coccè V, Bonomi A, Ami D, Ceccarelli P, Ciusani E, Viganò L, Locatelli A, Sisto F, Doglia SM, *et al*: Paclitaxel is incorporated by mesenchymal stromal cells and released in exosomes that inhibit in vitro tumor growth: A new approach for drug delivery. J Control Release 192: 262-270, 2014.
238. Bonomi A, Sordi V, Dugnani E, Ceserani V, Dossena M, Coccè V, Cavicchini L, Ciusani E, Bondiolotti G, Piovani G, *et al*: Gemcitabine-releasing mesenchymal stromal cells inhibit in vitro proliferation of human pancreatic carcinoma cells. Cytotherapy 17: 1687-1695, 2015.
239. van der Meel R, Fens MH, Vader P, van Solinge WW, Eniola-Adefeso O and Schiffelers RM: Extracellular vesicles as drug delivery systems: Lessons from the liposome field. J Control Release 195: 72-85, 2014.
240. Clayton A, Harris CL, Court J, Mason MD and Morgan BP: Antigen-presenting cell exosomes are protected from complement-mediated lysis by expression of CD55 and CD59. Eur J Immunol 33: 522-531, 2003.
241. Gomes-da-Silva LC, Fonseca NA, Moura V, Pedroso de Lima MC, Simões S and Moreira JN: Lipid-based nanoparticles for siRNA delivery in cancer therapy: Paradigms and challenges. Acc Chem Res 45: 1163-1171, 2012.
242. Simões S, Filipe A, Faneca H, Mano M, Penacho N, Düzgünes N and de Lima MP: Cationic liposomes for gene delivery. Expert Opin Drug Deliv 2: 237-254, 2005.
243. Willingham SB, Volkmer JP, Gentles AJ, Sahoo D, Dalerba P, Mitra SS, Wang J, Contreras-Trujillo H, Martin R, Cohen JD, *et al*: The CD47-signal regulatory protein alpha (SIRPa) interaction is a therapeutic target for human solid tumors. Proc Natl Acad Sci USA 109: 6662-6667, 2012.
244. Mendt M, Kamerkar S, Sugimoto H, McAndrews KM, Wu CC, Gagea M, Yang S, Blanko EVR, Peng Q, Ma X, *et al*: Generation and testing of clinical-grade exosomes for pancreatic cancer. JCI insight 3: e99263, 2018.
245. Bardol T, Dujon AM, Taly V, Dunyach-Remy C, Lavigne JP, Costa-Silva B, Kurma K, Eslami-S Z, Cayrefourcq L, Canivet C, *et al*: Early detection of pancreatic cancer by liquid biopsy 'PANLIPSY': A french nation-wide study project. BMC Cancer 24: 709, 2024.
246. Wei MY, Shi S, Liang C, Meng QC, Hua J, Zhang YY, Liu J, Zhang B, Xu J and Yu XJ: The microbiota and microbiome in pancreatic cancer: More influential than expected. Mol Cancer 18: 97, 2019.

247. Riquelme E, Zhang Y, Zhang L, Montiel M, Zoltan M, Dong W, Quesada P, Sahin I, Chandra V, San Lucas A, *et al*: Tumor microbiome diversity and composition influence pancreatic cancer outcomes. Cell 178: 795-806.e12, 2019.
248. Zhang X, Liu Q, Liao Q and Zhao Y: Pancreatic cancer, gut microbiota, and therapeutic efficacy. J Cancer 11: 2749-2758, 2020.
249. Jiang Z, Mou Y, Wang H, Li L, Jin T, Wang H, Liu M and Jin W: Causal effect between gut microbiota and pancreatic cancer: A two-sample Mendelian randomization study. BMC Cancer 23: 1091, 2023.
250. Kartal E, Schmidt TSB, Molina-Montes E, Rodríguez-Perales S, Wirbel J, Maistrenko OM, Akanni WA, Alashkar Alhamwe B, Alves RJ, Carrato A, *et al*: A faecal microbiota signature with high specificity for pancreatic cancer. Gut 71: 1359-1372, 2022.
251. McAllister F, Khan MAW, Helmink B and Wargo JA: The Tumor microbiome in pancreatic cancer: Bacteria and beyond. Cancer Cell 36: 577-579, 2019.
252. Kabwe M, Dashper S and Tucci J: The Microbiome in pancreatic cancer-implications for diagnosis and precision bacteriophage therapy for this low survival disease. Front Cell Infect Microbiol 12: 871293, 2022.
253. Chow YC, Yam HC, Gunasekaran B, Lai WY, Wo WY, Agarwal T, Ong YY, Cheong SL and Tan SA: Implications of *Porphyromonas gingivalis* peptidyl arginine deiminase and gingipain R in human health and diseases. Front Cell Infect Microbiol 12: 987683, 2022.
254. Maekawa T, Fukaya R, Takamatsu S, Itoyama S, Fukuoka T, Yamada M, Hata T, Nagaoka S, Kawamoto K, Eguchi H, *et al*: Possible involvement of Enterococcus infection in the pathogenesis of chronic pancreatitis and cancer. Biochem Biophys Res Commun 506: 962-969, 2018.
255. Zhou X, Xie F, Wang L, Zhang L, Zhang S, Fang M and Zhou F: The function and clinical application of extracellular vesicles in innate immune regulation. Cell Mol Immunol 17: 323-334, 2020.
256. Lai RC, Yeo RW, Tan KH and Lim SK: Exosomes for drug delivery-a novel application for the mesenchymal stem cell. Biotechnol Adv 31: 543-551, 2013.
257. Otsuka M and Kotani A: Recent advances in extracellular vesicles in gastrointestinal cancer and lymphoma. Cancer Sci 114: 2230-2237, 2023.
258. Vosough P, Khatami SH, Hashemloo A, Tajbakhsh A, Karimi-Fard F, Taghvimi S, Taheri-Anganeh M, Soltani Fard E, Savardashtaki A and Movahedpour A: Exosomal lncRNAs in gastrointestinal cancer. Clin Chim Acta 540: 117216, 2023.
259. Tang XH, Guo T, Gao XY, Wu XL, Xing XF, Ji JF and Li ZY: Exosome-derived noncoding RNAs in gastric cancer: Functions and clinical applications. Mol Cancer 20: 99, 2021.