Dual role of exosomes in pancreatic cancer: Underlying mechanisms and research advances (Review)

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Abstract. Pancreatic cancer is one of the most common malignant tumors. Due to late diagnosis and a lack of effective treatments, pancreatic cancer has a poor prognosis and a high mortality rate. Further understanding of the mechanisms underlying the development and progression of pancreatic cancer is key to developing rational diagnostic and therapeutic strategies. Exosomes are small vesicles secreted by most cells, carrying a rich cargo of lipids, proteins and nucleic acids. Exosomes serve various roles in intercellular communication, biological processes and signal transduction. Notably, exosomes exhibit a dual role in pancreatic cancer: Exosomes can directly promote tumor cell proliferation, growth and metastasis, modulate the complex immunosuppressive microenvironment and contribute to chemoresistance; by contrast, exosomes can serve as biomarkers for diagnosis and drug delivery vehicles. The present study systematically reviewed the mechanisms through which exosomes exert their dual functions via their specific biomolecular cargo in pancreatic cancer, as well as their potential applications in diagnosis and treatment, thereby laying a research foundation for exosomes to potentially serve a more active role in pancreatic cancer in the future.

Contents

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1. Introduction

Pancreatic cancer (PC) is a fatal disease, with ~51,980 deaths in the US each year and a 5-year survival rate of only 13%, making it a malignancy with one of the worst prognosis among all cancer types (1). Currently, the primary clinical treatments for PC include surgical resection and chemotherapy. However, due to the aggressive progression of the disease and the fact that ~80% of patients are diagnosed at an advanced stage, surgical resection is often not feasible (2). Even the modified version of folinic acid, irinotecan and oxaliplatin (mFOLFIRINOX) chemotherapy regimen, which is considered one of the most effective treatments for PC, achieves a 3-year overall survival rate of merely 63.4% (3). mFOLFIRINOX is an effective combined chemotherapy regimen. The name is derived from the abbreviations of its four constituent drugs: FOL, FIRI and NOX. The prefix 'm' indicates 'improved'. This regimen was developed by the classic FOLFIRINOX protocol. Currently, it is mainly used as a first-line treatment option for patients with good physical condition who have locally advanced or metastatic PC. FOLFIRINOX is currently one of the key chemotherapy regimens in the field of PC. However, chemotherapy for PC is often limited by two major challenges: The development of chemoresistance, which prevents patients from completing the full course of treatment and the cumulative toxicity of prolonged regimens. Therefore, both treatment efficacy and quality of life of patients are compromised (4). The exact etiology of PC remains to be elucidated; however, the tumor microenvironment (TME), environmental factors and genetic predisposition are recognized as major contributors to its initiation and progression (5). For instance, smoking is the primary non-genetic factor associated with an increased risk of pancreatic ductal adenocarcinoma (PDAC), with an odds ratio of 3.7 (95% confidence interval: 1.8-7.6) (6). Additionally, smoking is significantly associated with a notable decrease in the average age of diagnosis among patients with familial PDAC. These findings underscore the critical role of smoking-related environmental factors in the pathogenesis and progression of PDAC (7,8). The TME of PC consists of cancer, stromal and immune cells and extracellular matrix

components, all of which serve key roles in promoting tumor growth and metastasis (9). Key features include driver gene mutations in cancer cells, excessive collagen and extracellular matrix deposition by stromal cells leading to tissue fibrosis and markedly expressed inflammatory cytokines that create a pro-inflammatory and immunosuppressive milieu. This unique TME not only presents a notable barrier to treatment but also offers potential targets for novel therapeutic strategies. Therefore, developing early diagnostic methods and effective treatments for PC remains an urgent and key challenge.

Exosomes are a type of extracellular vesicle (EV) with a diameter of 30-150 nm. Exosomes carry a diverse cargo of lipids, proteins and nucleic acids (10), enabling them to serve as exceptional messengers for complex information transfer between cells (11), across distant tissues (12) and between tumor and stromal compartments (13). Exosomes are present in nearly all bodily fluids, including blood, sweat, tears, urine, saliva, breast milk, ascites and cerebrospinal fluid. Exosomes derived from different sources can exert distinct effects on tumors (14). Tumor-derived exosomes can transfer oncogenic molecules (15), promote anti-apoptotic effects (16), stimulate angiogenesis (17) and alter tumor cell metabolism (18), thereby facilitating tumor growth. However, a previous study has also demonstrated that exosomes hold promise as biomarkers for the early diagnosis of PC (19). Furthermore, exosomes can serve as notable drug delivery vehicles, offering potential therapeutic strategies for an extensive subset of patients with PC with chemoresistance (20). Furthermore, elucidating the interrelationship between the TME of PC and exosomes may help researchers identify novel therapeutic targets, thereby opening novel avenues for treatment. Thus, exosomes serve a dual role in PC. The present review aims to summarize the mechanisms underlying the dual functions of exosomes in the initiation and progression of PC, provide novel insights and directions in optimally utilizing exosomes in clinical therapy and accelerate the clinical translation of exosome-based targeted therapies for PC.

2. Exosomes

Origin and isolation of exosomes. In 1946, Chargaff and West (21) identified a coagulation factor resembling thromboplastic protein in the blood of patients with hemophilia and bleeding disorders, which is considered the starting point of the field of EV biology. Currently, EVs are categorized into three types based on their diameter and release mechanisms: Exosomes (30-150 nm), microvesicles (100-1,000 nm) and apoptotic bodies (500-5,000 nm), exosomes, which are released upon fusion of multivesicular bodies with the plasma membrane; microvesicles, which bud directly from the plasma membrane; and apoptotic bodies, which are generated during apoptosis via cell membrane blebbing. These three types of vesicles differ in size, formation mechanisms and biological functions, collectively serving as important mediators of intercellular communication (Fig. 1). Exosomes, a type of EV, were identified in 1981 by Trams *et al* (22) in the supernatant of cultured sheep reticulocytes. In 1987, Johnstone *et al* (23) named them 'exosomes'. The cellular origin and purity of exosomes serve a key role in processes such as the occurrence, metastasis and drug resistance of PC. Therefore, the development of efficient and specific techniques for the isolation and extraction of exosomes is of notable importance for research on the mechanisms of PC and its clinical applications. Several exosome isolation techniques have been developed to date, including ultracentrifugation (24), ultrafiltration (25), size-exclusion chromatography (26), precipitation-based isolation (27), immunoaffinity capture (28) and microchip-based technology (29). Each of these techniques has its own principles, advantages and disadvantages (30). However, each technique has certain limitations and fails to meet the expectations of being efficient, high in purity, simple and low in cost. Therefore, the effective, accurate and efficient isolation of high-purity exosomes remains a major challenge (31).

Biogenesis and composition of exosomes. The biogenesis and synthesis of exosomes is a complex process, which begins with endocytosis at the cell membrane surface, where early endosomes are formed through inward budding. Over time, early endosomes mature into late endosomes. Late endosomes primarily form intraluminal vesicles (ILVs) through three pathways: Endosomal sorting complex required for transport, tetraspanin proteins and ceramide induction, and these ILVs gradually develop into multivesicular bodies (MVBs) (32-34). Subsequently, most MVBs fuse with lysosomes, leading to the degradation of ILVs, while a small number of MVBs fuse with the plasma membrane and release exosomes into the extracellular environment (32,35,36). Exosomes carry a rich cargo of lipids, proteins and nucleic acids. The lipid components in exosomes include cholesterol, sphingomyelin, glycosphingolipids, phosphatidylserine, phosphatidylinositol, phosphatidic acid and ceramide (37). Common proteins in exosomes include those associated with membrane transport, such as Ras-related in brain GTPases, annexins, flotillins and MVB biogenesis proteins including apoptosis-linked gene 2-interacting protein X (38). Exosomes also contain tetraspanin proteins, including CD9, CD63 and CD81, as well as heat shock proteins (HSP) such as HSP60 and HSP90. The nucleic acid components in exosomes are also highly diverse, such as microRNA (miRNA/miR) and messenger RNA, which were among the first two types identified (39,40), followed by long non-coding RNA (lncRNA), transfer RNA, small nuclear RNA and circular RNA (circRNA/circ) (39,41) (Fig. 2). These RNA not only act as regulators of gene expression but also serve as potential biomarkers (42). For instance, miR-141 can be detected in the blood of patients with prostate cancer, and its expression level is correlated with the size and malignancy of the tumor (43). Saliva miR-3679-5p and miR-940 have good discriminatory ability and can be used for the detection of resectable PC, with reasonable specificity and sensitivity (44). Furthermore, lncRNA can be regarded as an independent predictor of pathological cardiac remodeling and diastolic dysfunction in patients with type 2 diabetes (45).

3. 'Dark side' of exosomes: Promoting the initiation and progression of PC

Exosomes serve a non-negligible 'dark' role in the initiation and progression of PC, driving tumor development and inducing therapy resistance through multiple mechanisms. Specifically, exosomes serve as key mediators of intercellular communication and can be derived from various cell types, including PC cells, adipocytes, cancer-associated fibroblasts (CAFs) and

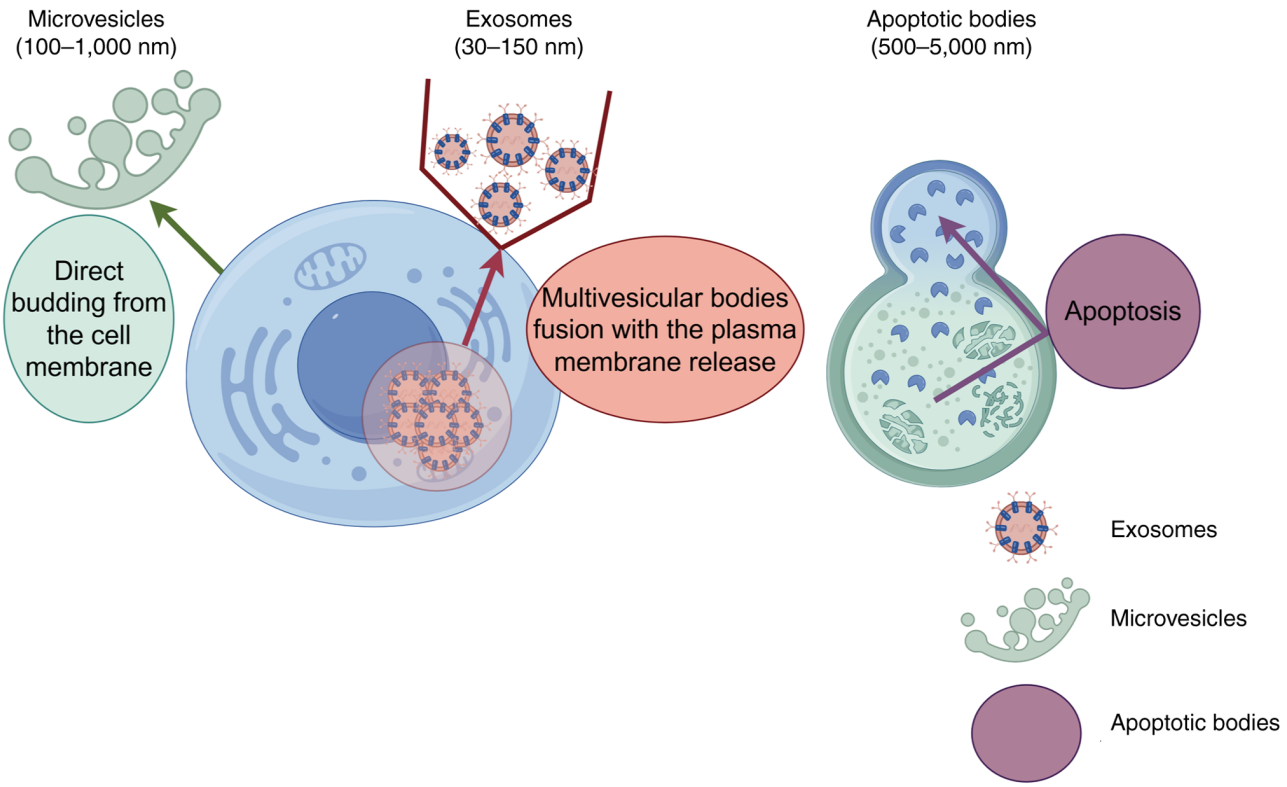

Figure 1. Classification of extracellular vesicles. Green arrows indicate microvesicles (100-1,000 nm), which bud directly from the cell membrane; red arrows indicate exosomes (30-150 nm), which are released upon fusion of multivesicular bodies with the plasma membrane; and purple arrows indicate apoptotic bodies (500-5,000 nm), which are released during apoptosis.

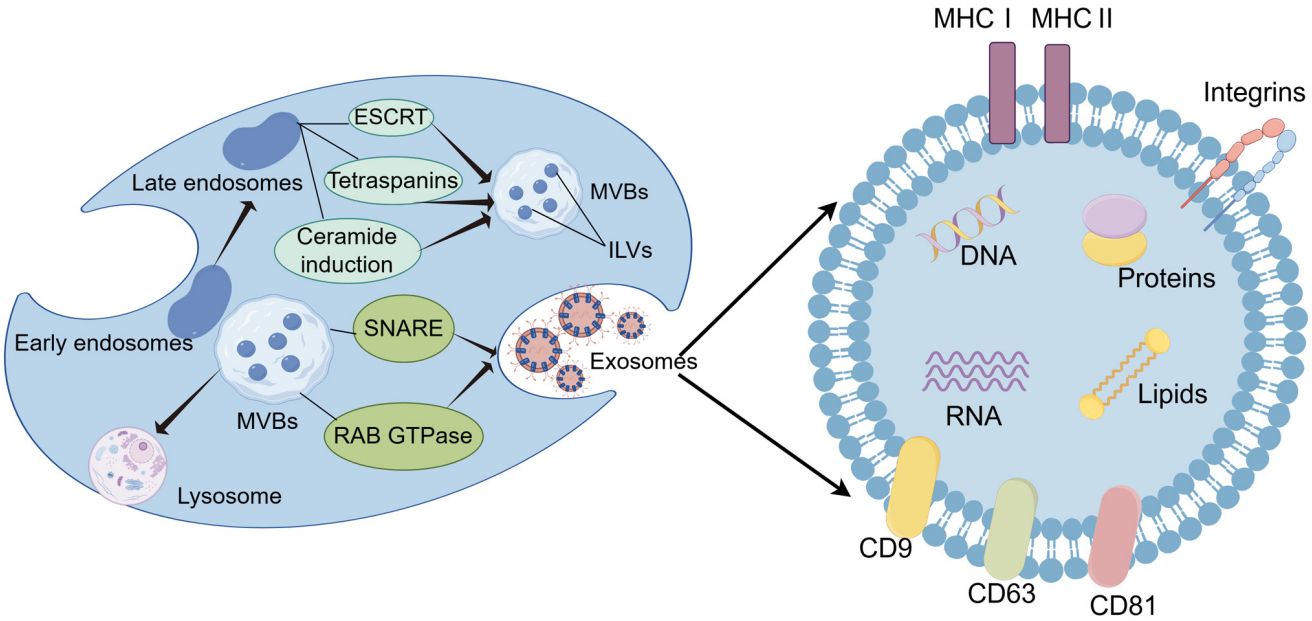

Figure 2. Biogenesis and composition of exosomes. Black arrows indicate the molecular mechanisms and trafficking pathways involved in exosome biogenesis and release. Exosomes originate from early endosomes, which progressively mature into late endosomes. Late endosomes undergo inward budding to form ILVs through ESCRT-dependent mechanisms, tetraspanins and ceramide-induced pathways, resulting in the generation of MVBs. MVBs have two distinct fates: Fusion with lysosomes for degradation or fusion with the plasma membrane via RAB GTPases and SNARE proteins to release exosomes. The released exosomes carry diverse molecular cargo, including MHC class I/II molecules, integrins, proteins, lipids, RNA and tetraspanins (CD9, CD63, CD81). ESCRT, endosomal sorting complex required for transport; MVBs, multivesicular bodies; ILV, intraluminal vesicles; MHC, major histocompatibility complex; RAB GTPase, Ras-related in brain; SNARE, soluble N-ethylmaleimide-sensitive factor activating protein receptor.

immune cells (46,47). By carrying specific molecules such as miRNAs, proteins and circRNAs, exosomes activate multiple signaling pathways [such as signal transducer and activator of transcription 3 (STAT3), hypoxia inducible factor 1α (HIF-1α),

epidermal growth factor receptor/mitogen-activated protein kinase (EGFR/MAPK)], directly promoting tumor cell proliferation, invasion and metastasis. Simultaneously, exosomes act as key modulators of the immunosuppressive TME. Exosomes can induce M2 macrophage polarization and regulate pathways such as protein kinase B/extracellular signal-regulated kinase (AKT/ERK), establishing a local environment conducive to immune evasion and tumor metastasis. Furthermore, exosomes notably contribute to chemoresistance. They can function as drug efflux pumps or deliver miRNAs (such as miR-155 and miR-210) to inhibit apoptosis and ferroptosis, thereby mediating resistance to gemcitabine. Furthermore, exosomes can also promote the progression of PC by regulating lipid metabolism and the TME (Table I) (48-66). These findings not only highlight exosomes as key drivers of malignant progression in PC but also provide a theoretical basis in targeting them to reverse drug resistance and improve therapeutic efficacy (Fig. 3).

Drives tumor growth and cell proliferation. Exosomes can drive the proliferation of tumor cells through multiple signaling pathways. The mechanism of their action mainly involves exosomes derived from tumor cells, CAFs and immune cells. A previous study using *in vitro* cell models reported that exosomes derived from cancer-associated adipocytes generated by co-culturing human adipocytes with human PC cells could promote the proliferation, invasion, migration and drug resistance of PC cells through the suppressor of cytokine signaling 7/STAT3/serum amyloid A1 pathway (48). Similarly, Zhang *et al* (49) reported that exosomes derived from CAFs could promote the proliferation of PC cells by regulating Abelson murine leukemia viral oncogene homolog 2 through miR-224-3p. Based on an *in vivo* animal model study, Zhou *et al* (50) reported that exosomes derived from CAFs could also exert effects through the silent information regulator 3/histone 3 lysine 9 acetylation/HIF-1α axis.

By contrast, exosomes secreted by PC cells themselves also serve a key role in tumor progression. For example, miR-519a/522-5p in exosomes can promote PC progression by enhancing the Warburg effect (51), miR-3960 promotes the proliferation, invasion and metastasis of PC cells through the transcription factor activator protein-2α axis (52), and the DnaJ heat shock protein family (HSP40) member B11 protein participates in PC progression by regulating the EGFR/MAPK pathway (53). Furthermore, exosomes derived from immune cells also regulate the progression of PC. For instance, miR-202-5p and miR-142-5p in exosomes derived from macrophages can enhance the invasiveness of PC cells and promote the metastasis of pancreatic ductal adenocarcinoma (54). In addition, exosomes derived from M2-type macrophages can further support tumor growth by targeting E2F transcription factor 2 and inducing tumor angiogenesis (55). These results collectively indicated that exosomes can jointly serve a role in promoting the occurrence and development of PC through various mechanisms.

Shapes the immunosuppressive microenvironment. The mechanism by which exosomes promote the progression of PC by shaping an immunosuppressive microenvironment has been a notable research direction in this field. Although existing studies have revealed the relevant pathways, the strength of the evidence varies, mainly based on *in vitro* cell models or *in vivo* animal models. In *in vitro* cell models, it has been reported that exosomes derived from PC cells can induce M2-type macrophage polarization by delivering miR-510 and lncRNA FGD5-AS1, thereby enhancing the vitality, migration and invasion of cancer cells (56,57). In *in vivo* animal models, the relevant mechanisms of action have been further verified and expanded. For example, Yang *et al* (58) reported that exosomes derived from CAFs can carry prostaglandin-endoperoxide synthase 2 and induce M2-type macrophage polarization by activating the nucleotide-binding oligomerization domain-containing protein 1, thereby promoting the metastasis of PC. The exosomes of tumor-associated macrophages, through the tyrosine kinase-binding protein, promote the metastasis process of PC via the CD44/AKT/ERK pathway (59). These results revealed the multi-cellular origin and multi-pathway synergy of exosomes in shaping the immunosuppressive microenvironment, providing key clues for further understanding of the progression mechanism of PC.

Induces therapy resistance. PC is prone to develop treatment resistance at an early stage, markedly threatening the life and quality of life of patients. Currently, the mechanism of drug resistance in PC has not been fully elucidated, but exosomes may serve a key role in this process. Exosomes may mediate PC resistance through multiple pathways (67). They can either remove drugs from cancer cells directly or deliver miRNA mutations or upregulated proteins to drug-sensitive cells to exert an indirect effect (20,68,69). The drug resistance mechanism of exosomes has been further clarified in different research models. *In vitro* cell models have demonstrated that exosomes derived from PC cells can upregulate STAT3 expression by inhibiting miR-298 through protein phosphatase 3 catalytic subunit β (60). Furthermore, exosomes can induce the high expression level of ATP-binding cassette sub-family G member 2 as a drug efflux pump in cells *in vitro* (61). The miR-210 in exosomes derived from PC stem cells can trigger the mTOR signaling pathway, thereby inducing gemcitabine resistance (62).

In vivo animal models have further identified that exosomes derived from CAFs can inhibit ferroptosis by mediating the acyl-CoA synthetase long-chain family member 4 pathway through miR-3173-5p, thereby enhancing the resistance of PC cells to gemcitabine (63). Of note, the clinical sample analysis supported the hypothesis that exosomes derived from PC cells, carrying miR-155, target tumor protein 53 inducible nuclear protein 1 and inhibit apoptosis, thereby contributing to the drug resistance mechanism (64). These findings revealed the multi-level and multi-pathway regulatory role of exosomes in PC resistance, providing notable evidence in further understanding of the resistance mechanism and the development of reversal strategies.

Regulates lipid metabolism and the TME. Exosomes participate in metabolic reprogramming and immune microenvironment remodeling in PC by delivering lipid metabolism-related molecules. For instance, previous research indicated that the fatty acid binding protein 7 in macrophages can transfer the induced lipids to $CD8^+$ T cells and tumor cells through exosomes. This process leads to dysfunction of $CD8^+$ T cells and proliferation of tumor cells through metabolic reprogramming (65). Furthermore, a previous study demonstrated that the medium-chain acyl-CoA dehydrogenase present in

Table I. Role of exosomes in the pathogenesis and progression of PC.

A, Exosomes drive tumor growth and tumor cell proliferation		
Cellular origins of exosomes	Specific mechanisms of action	(Refs.)
CAAs	miR-199a-3p mediates the SOCS7/STAT3/SAA1 pathway	(48)
CAFs	miR-224-3p regulates ABL2; miR-421 functions through the SIRT3/H3K9Ac/HIF-1α axis	(49,50)
PC cells	miR-519a/522-5p enhances the Warburg effect; miR-3960 mediates the TFAP2A axis; DNAJB11 protein regulates the EGFR/MAPK pathway	(51-53)
Macrophages	miR-202-5p and miR-142-5p enhance the invasive ability of PC cells	(54)
M2 type macrophages	Targeting E2F2 promotes tumor angiogenesis	(55)
B, Exosomes shape the immunosuppressive microenvironment		
Cellular origins of exosomes	Role of exosomes in PC	(Refs.)
PC cells	miR-510 and lncRNA FGD5-AS1 promote M2 macrophages polarization	(56,57)
CAFs	Carrying PTGS2 activates the NOD1 and induces M2 macrophages polarization	(58)
Tumor-associated macrophages	TYROBP mediates the CD44/AKT/ERK pathway	(59)
C, Exosomes for induction therapy resistance		
Cellular origins of exosomes	Role of exosomes in PC	(Refs.)
PC cells	PPP3CB inhibits miR-298 and upregulates STAT3 expression; ABCG2 is induced to function as a drug efflux pump *in vitro*; miR-155 targets TP53INP1 to confer anti-apoptotic activity	(60,61,64)
PC stem cells	miR-210 triggers the mTOR signaling pathway	(62)
CAFs	miR-3173-5p mediates the ACSL4 pathway to inhibit ferroptosis	(63)
D, Exosomes for the regulation of lipid metabolism and the TME		
Cellular origins of exosomes	Role of exosomes in PC	(Refs.)
Macrophages	Through metabolic reprogramming, $CD8^+$ T-cell function is impaired and tumor cell proliferation is promoted	(65)
PC cells	ACADM regulates fatty acid metabolism and ferroptosis	(66)

CAAs, cancer-associated adipocytes; CAFs, cancer-associated fibroblasts; SOCS7/STAT3/SAA1, suppressor of cytokine signaling 7/signal transducer and activator of transcription 3/serum amyloid A1; miR, microRNA; SIRT3/H3K9Ac/HIF-1α, silent information regulator 3/histone 3 lysine 9 acetylation/hypoxia inducible factor 1α; PC, pancreatic cancer; TFAP2A, transcription factor activator protein-2α; E2F2, E2F transcription factor 2; PTGS2, prostaglandin-endoperoxide synthase 2; TYROBP, tyrosine kinase-binding protein; ABCG2, ATP-binding cassette transporter G2; ACSL4, acyl-CoA synthetase long-chain family member 4; TME, tumor microenvironment; ACADM, medium-chain acyl-CoA dehydrogenase; TP53INP1, tumor protein 53 inducible nuclear protein 1; DNAJB11, DnaJ heat shock protein family (HSP40) member B11 protein; lncRNA, long non-coding RNA; NOD1, nucleotide-binding oligomerization domain-containing protein 1; PPP3CB, protein phosphatase 3 catalytic subunit β.

exosomes enhances gemcitabine resistance by regulating fatty acid metabolism and ferroptosis in PC (66). These findings indicated that exosomes serve not only as carriers but also as key mediators of lipid metabolic reprogramming, indirectly regulating the immunosuppressive state of the TME through metabolic intervention.

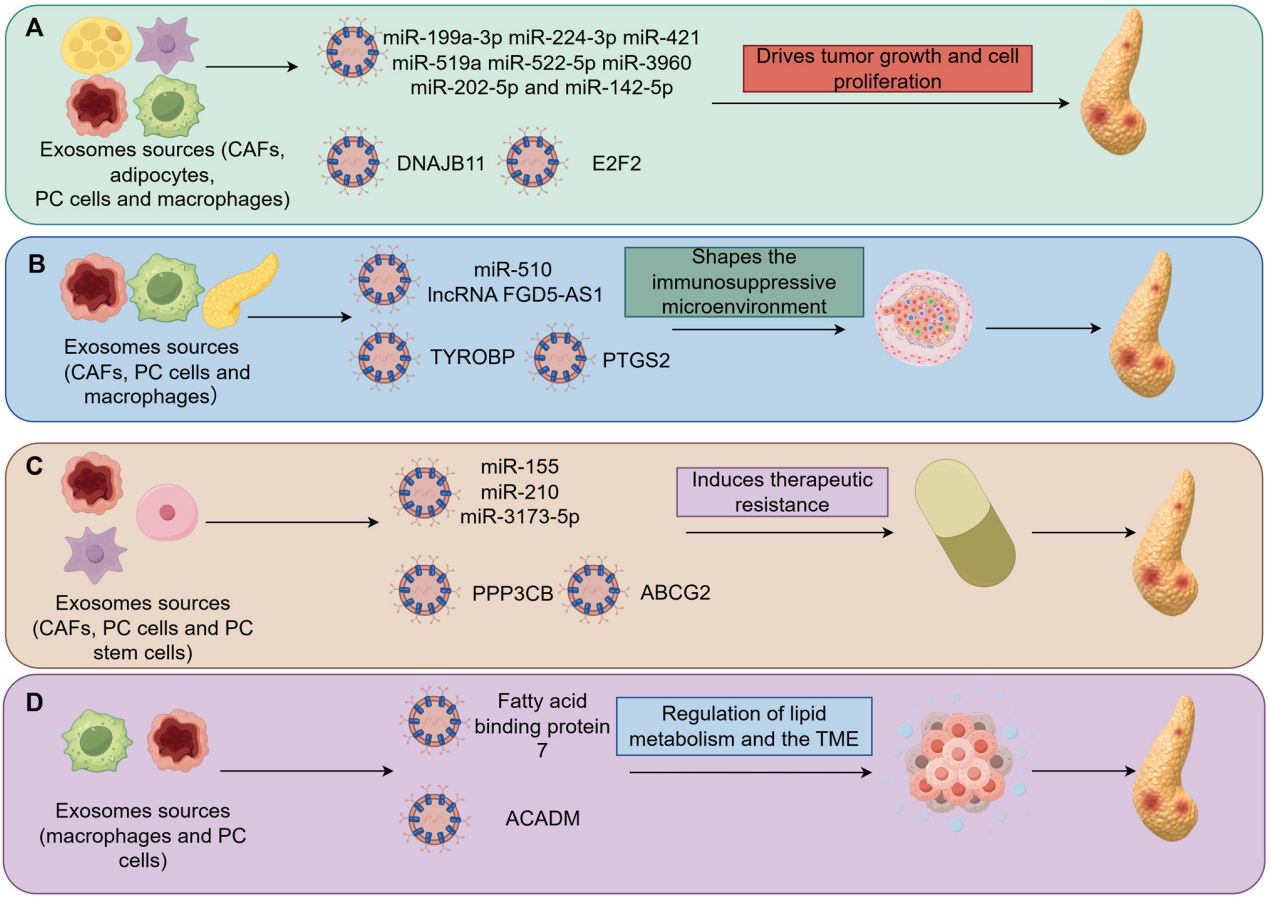

Figure 3. Mechanisms of exosomes in promoting the initiation and progression of PC. Black arrows indicate the cellular sources of exosomes and their mediated biological functions. Exosomes derived from CAFs, adipocytes, macrophages, PC cells and PC stem cells carry diverse cargos, including miRNAs (miR-199a-3p, miR-224-3p, miR-421, miR-519a, miR-522-5p, miR-3960, miR-202-5p, miR-142-5p, miR-510, miR-155, miR-210, miR-3173-5p), lncRNA FGD5-AS1 and proteins (DNAJB11, E2F2, TYROBP, PTGS2, PPP3CB, ABCG2, ACADM, fatty acid binding protein 7). These exosomal cargos contribute to PC progression through multiple mechanisms: (A) Driving tumor growth and cell proliferation, (B) shaping the immunosuppressive microenvironment, (C) inducing therapeutic resistance, and (D) regulating lipid metabolism and the TME. CAFs, cancer-associated fibroblasts; PC, pancreatic cancer; DNAJB11, DNA J homolog subfamily B member 11; E2F2, E2F transcription factor 2; miR, microRNA; lncRNA, long non-coding RNA; lncRNA FGD5-AS1, FGD5 antisense RNA 1; PTGS2, prostaglandin-endoperoxide synthase 2; TYROBP, tyrosine kinase-binding protein; PPP3CB, protein phosphatase 3 catalytic subunit β isoform; ABCG2, ATP-binding cassette transporter G2; ACADM, medium-chain acyl-CoA dehydrogenase; TME, tumor microenvironment.

Although exosomes serve an undeniable 'dark side' role in the occurrence and development of PC, they can promote disease progression by directly driving tumor growth and cell proliferation, shaping an immunosuppressive microenvironment and inducing treatment resistance. However, its unique biological characteristics also provide a novel 'bright side' role for the treatment of PC. This duality of opposites lays the foundation for its transformation from a disease promoter to a diagnostic and therapeutic tool. Based on further understanding of the mechanism of action of exosomes in PC, researchers are actively developing their application potential in early diagnosis, targeted therapy and drug resistance reversal, thereby maximizing the positive role of exosomes in PC. The following section systematically elaborates on the latest research progress of exosomes as diagnostic markers, direct therapeutic tools and drug delivery carriers.

4. 'Bright side' of exosomes: Potential for diagnosis and treatment of PC

In recent years, exosomes have demonstrated notable 'bright side' potential in the diagnosis and treatment of PC. In terms of diagnosis, due to the protective effects of their lipid bilayer membrane and the CD47 transmembrane protein, exosomes carrying PC-specific information remain relatively stable in the circulatory system and are less susceptible to clearance by monocytes. This stability provides a possibility for early diagnosis through liquid biopsy (70-72). Regarding therapeutic applications, exosomes exhibit a key role: i) Exosomes can function as natural therapeutic agents originating directly from immune cells or stem cells, capable of effectively inhibiting tumor cell proliferation and selectively killing cancer cells; ii) exosomes represent a highly promising class of drug delivery vehicles. By loading chemotherapeutic drugs or immunomodulators, exosomes enable precise targeting to overcome drug resistance and reprogram the TME, thereby offering notable potential for effective PC treatment; and iii) exosomes can exert an active effect through the 'exosome-lipid metabolism-TME' axis (Table II) (73-86) (Fig. 4).

Exosomes as a biomarker for liquid biopsy. In recent years, exosomes have demonstrated potential to serve as a biomarker for the early diagnosis of PC. Several studies based on clinical samples have systematically verified their value. In 2022,

Table II. Role of exosomes in the diagnosis and treatment of PC.

A, Exosomes as a biomarker for liquid biopsy		
Cellular origins of exosomes	Specific molecules and mechanisms of action	(Refs.)
Serum	$CD63^+$ cells; miR-451a; GPRC5C; EPS8	(73-75)
Platelet	$CD41^+$ and $CD61^+$ cells	(73)
Plasma	hsa_circ_0001666 and hsa_circ_0006220	(76)
Duodenal fluid	miR-20a	(77)
B, Exosomes as a direct tool in treating PC		
Cellular origins of exosomes	Specific molecules and mechanisms of action	(Refs.)
NK cells	Upregulates the expression level of let-7b-5p in PC cells and inhibits tumor cell proliferation by targeting the cell cycle regulator CDK6	(78)
Islet derived progenitor cells	Selectively kills PC cells without causing harm to normal cells	(79)
UC-NK cells	Enters PANC-1 cells via endocytosis, induces mitochondrial oxidative damage and suppresses PANC-1 cell progression	(80)
BMSCs	miR-124 exhibits anti-PC activity	(81)
C, Exosomes as a carrier for drug delivery		
Cellular origins of exosomes	Specific molecules and mechanisms of action	(Refs.)
BMSCs	Loaded with gemcitabine, it enhances apoptosis and inhibits the proliferation of PC cells	(82)
M1 type macrophages	Loaded with gemcitabine and deferasirox, it overcomes inherent drug resistance	(83)
PC cells	Loaded with gemcitabine, it markedly promotes drug uptake in cancer cells	(84)
D, 'Exosomes-lipid metabolism-TME' therapeutic strategies		
Cellular origins of exosomes	Specific molecules and mechanisms of action	(Refs.)
M1 type macrophages	Inhibits the lipid metabolism pathway, thereby reducing the proliferation, migratory and invasive abilities of PC cells and simultaneously promoting their apoptosis	(85)
PC cells	Involved in lipid metabolism and regulating the TME	(86)

GPRC5C, G protein-coupled receptor class C group 5 member C; EPS8, epidermal growth factor receptor pathway substrate 8; PC, pancreatic cancer; UC-NK, umbilical cord blood natural killer; BMSCs, bone marrow mesenchymal stem cells; TME, tumor microenvironment; miR, microRNA; hsa_circ, *Homo sapiens* circular RNA.

Odaka *et al* (73) identified that $CD63^+$ cells in serum-derived exosomes and $CD41/CD61^+$ cells in platelet-derived exosomes serve as potential diagnostic biomarkers for pancreatic ductal adenocarcinoma. Furthermore, miR-451a in serum-derived exosomes (74), as well as G protein-coupled receptor class C group 5 member C and EGFR pathway substrate 8 (75) have been proposed as candidate markers for the early detection of PC. In the same year, further research revealed that high expression levels of circRNAs (hsa_circ_0001666 and hsa_circ_0006220) in plasma-derived exosomes also possess diagnostic value (76). miR-20a, which is present in exosomes derived from duodenal fluid, has also been proposed as a biomarker for pancreatic ductal adenocarcinoma (77). These findings were all based on systematic validation using clinical samples and had a high level of evidence strength.

Furthermore, in order to enhance the sensitivity and specificity of exosome detection, novel detection technologies are constantly emerging. For example, Li *et al* (87) constructed an immunoassay system based on a hierarchical surface-enhanced Raman scattering substrate, enabling highly sensitive detection of exosomes. The study identified that a novel combination of leucine-rich α-2-glycoprotein 1-derived

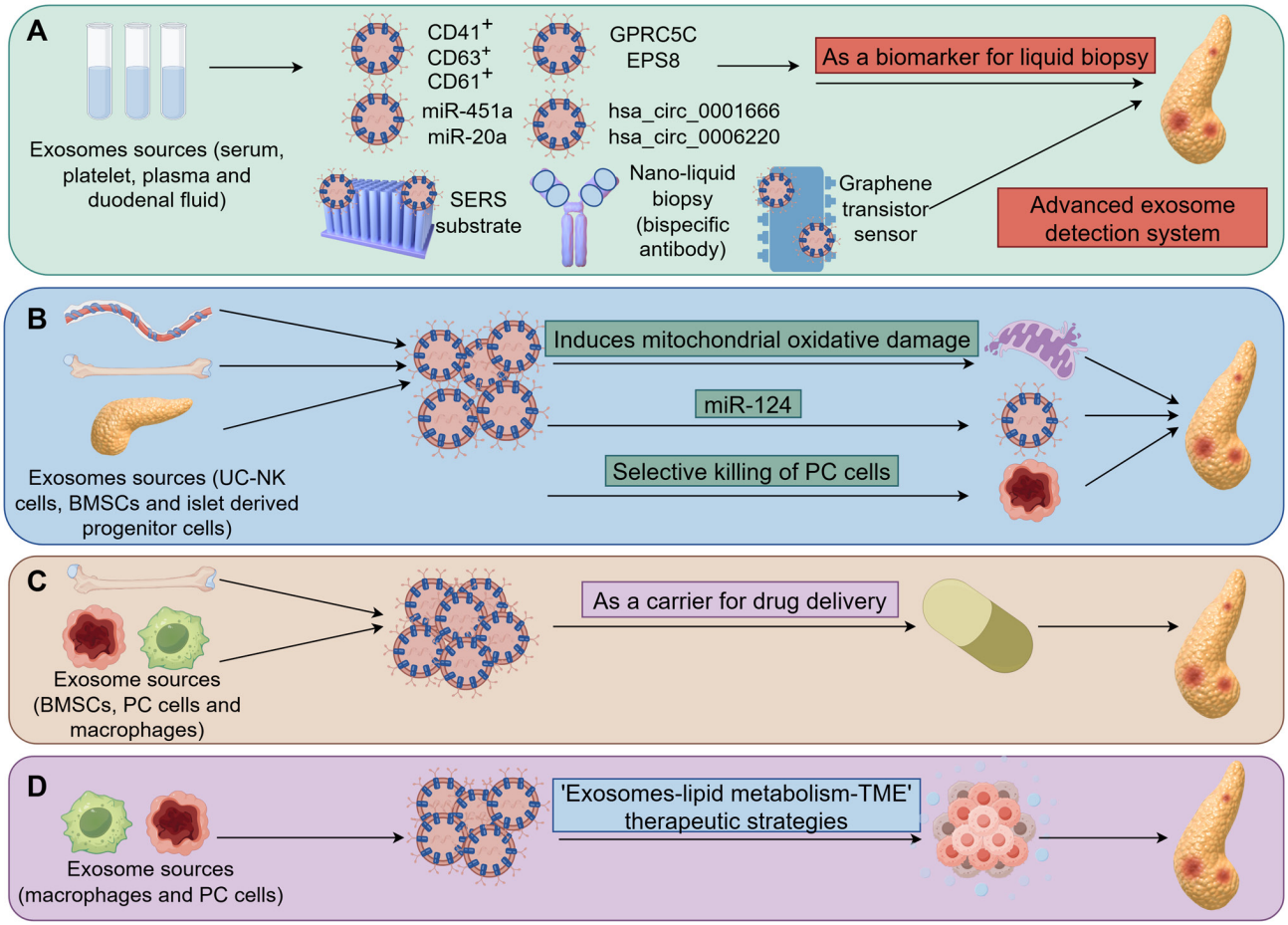

Figure 4. Mechanisms of exosomes in the diagnosis and treatment of PC. Black arrows indicate the multifaceted applications of exosomes in PC research. (A) Exosomes derived from serum, platelets, plasma and duodenal fluid carry various molecules, including CD41$^+$, CD63$^+$, CD61$^+$, GPRC5C, EPS8, miR-451a, miR-20a, hsa_circ_0001666 and hsa_circ_0006220, serving as biomarkers for liquid biopsy. Additionally, researchers have developed advanced exosome detection systems, such as nanoscale SERS substrates, graphene transistor sensors and bispecific antibody-based platforms, to improve the accuracy of early diagnosis. (B) Exosomes derived from UC-NK cells, BMSCs and islet-derived progenitor cells can directly kill PC cells through distinct mechanisms of action. (C) As drug delivery carriers, exosomes derived from BMSCs, PC cells and macrophages can be utilized for therapeutic agent delivery. (D) Regarding 'Exosomes-lipid metabolism-TME' therapeutic strategies, exosomes derived from macrophages and PC cells are involved in therapeutic interventions targeting this regulatory axis. PC, pancreatic cancer; SERS, surface-enhanced Raman spectroscopy; GPRC5C, G protein-coupled receptor class C group 5 member C; EPS8, epidermal growth factor receptor pathway substrate 8; UC-NK cells, umbilical cord blood natural killer cells; BMSCs, bone marrow mesenchymal stem cells; TME, tumor microenvironment; miR, microRNA; hsa_circ, *Homo sapiens* circular RNA.

exosomes and glypican-1-derived exosomes could enhance the diagnostic efficiency for PC. Yu *et al* (88) developed a simple nanoliquid biopsy method that achieves specific, ultrasensitive and cost-effective exosome detection through a dual-specific biomarker antigen co-recognition and capture strategy. Yin *et al* (89) designed a graphene field-effect transistor-based biosensor for accurate and rapid detection of PC-associated exosomes. These technological advancements have collectively facilitated the transformation of exosomes from biomarker identification to clinical application, providing a multi-level solution for the early diagnosis of PC.

Exosomes as a direct tool for the treatment of PC. Exosomes can serve as a direct therapeutic tool in inhibiting the development of PC and their effects have been verified through various research models. In *in vitro* cell models, exosomes derived from multiple cell sources exhibited clear antitumor activity. For instance, exosomes derived from natural killer cells can upregulate the expression level of let-7b-5p in PC cells and target the cell cycle regulatory factor CDK6, thereby inhibiting tumor cell proliferation (78). Furthermore, Hasoglu and Karatug Kacar (79) identified that exosomes derived from pancreatic islet progenitor cells can selectively kill PC cells without notable damage to normal cells, demonstrating good biological safety. In *in vivo* animal models, these therapeutic potentialities can be further verified. A previous study has demonstrated that exosomes derived from umbilical cord blood natural killer cells can enter PANC-1 cells through endocytosis, induce mitochondrial oxidative damage and inhibit the progression of this cell line, revealing a marked anti-PC effect (80). Furthermore, miR-124 contained in exosomes derived from bone marrow mesenchymal stem cells (BMSCs) has also exhibited anti-PC activity in both *in vitro* and *in vivo* experiments (81). These studies collectively demonstrated that exosomes have the potential for multi-mechanism synergy, extensive sources and good safety in the treatment of PC, providing notable basis for the development of novel biological therapies.

Exosomes as a carrier for drug delivery. Exosomes, as an efficient drug delivery carrier, are expected to provide a

safer and more effective delivery strategy for traditional anti-PC drugs due to their notable biocompatibility and low toxicity (90,91). An *in vitro* cell model study demonstrated that exosomes derived from human BMSCs carrying gemcitabine can enhance apoptosis to inhibit the proliferation of PC cells, thereby inhibiting the progression of PC (82). Furthermore, exosomes derived from M1-type macrophages loaded with gemcitabine and deferasirox can effectively overcome drug resistance and provide a potential effective treatment strategy for patients with PC with drug resistance (83). The *in vivo* animal models further demonstrated the therapeutic advantages of the exosome delivery system, autologous exosomes carrying gemcitabine can markedly promote the uptake of the drug in cancer cells and enhance its antitumor effect (84). Furthermore, the emerging engineered exosome platform offers a novel direction for the regulation of the TME; for instance, Sun *et al* (92) developed a novel exosome-based drug delivery platform, cmExo^{aCD11b}, aiming to precisely target and reprogram the TME for immunotherapy of PC. This technology can cause M2 macrophages to polarize to the M1 phenotype, thereby reprogramming the TME and markedly inhibiting the development of PC. These studies collectively demonstrated that exosomes not only serve as efficient drug carriers but can also achieve multi-mechanism synergistic antitumor effects through dynamic interactions with the TME.

'Exosomes-lipid metabolism-TME' therapeutic strategies. Of note, exosomes derived from M1-type macrophages can inhibit the lipid metabolism pathway, thereby reducing the proliferation, migratory and invasive abilities of PC cells, while simultaneously promoting their apoptosis (85). Furthermore, a previous study has demonstrated that exosomes may be involved in lipid metabolism and regulate the TME, thereby participating in multiple processes of PC (86). These findings provided novel insights in developing metabolism-targeted exosome-based therapies.

5. Challenges and future directions

In summary, the present review systematically elaborated on the dual roles of exosomes in PC and their specific mechanisms of action. Exosomes serve a positive role in the treatment of PC, however, their involvement in regulating PC cells, shaping an immunosuppressive microenvironment and promoting chemotherapy resistance remains to be explored in future research. Further exploration of the key molecules, proteins and signaling pathways underlying these adverse effects may provide novel research directions and intervention strategies for targeted therapy of PC.

However, numerous challenges remain in realizing the optimal application of exosomes for PC therapy. First, current techniques in isolating and extracting exosomes face notable limitations (93). Although multiple methods are available, such as ultracentrifugation and size-exclusion chromatography, a standardized protocol that simultaneously ensures high purity, simplicity and low cost is still lacking (94,95). Establishing a unified separation standard for exosomes is of notable importance for the reproducibility of research and cross-study comparisons. Second, the diameter of exosomes ranges from 30-150 nm, which is below the diffraction limit of conventional optical microscopy. This poses notable challenges in visualizing the release, transport and real-time dynamics of exosomes. In recent years, super-resolution microscopy holds promise in resolving exosomal ultrastructure; its high spatial resolution often comes at the expense of temporal efficiency, making dynamic studies in living cells particularly challenging (96,97). Third, the extraction of exosomes remains costly. While obtaining exosomes from patient urine or saliva is a non-invasive approach with certain practical advantages, the process is often time-consuming and requires notable financial investment (98). Of note, in recent years, EVs extracted from natural plants or food sources have successively demonstrated notable biocompatibility and therapeutic potential, providing a key direction and research breakthrough in reducing extraction costs and developing stable and controllable EV resources (99,100). Fourth, although exosomes exhibit notable promise as drug delivery vehicles, key issues such as high loss rates during drug loading and elevated production costs should be addressed (101). Currently, the use of serum-free culture systems to optimize the production process of exosomes, as well as the development of synthetic biomimetic vesicles with similar functions, provide a feasible technical direction in addressing these issues (102). Fifth, there is a notable lack of clinical data. Current research on exosome-based therapies for PC is largely limited to *in vitro* studies and *in vivo* mouse models. However, human clinical trials are still lacking (78,82,84). To promote its clinical application, the following key steps need to be clarified: i) Pharmacological and toxicological research are warranted to elucidate the pharmacokinetic and pharmacodynamic characteristics, biodistribution and potential immunogenicity of exosomes in the body; ii) in-depth clinical trials; and iii) progressive research from safety assessment to efficacy validation. Sixth, future studies should further elucidate how exosomes regulate the TME through lipid metabolism reprogramming, particularly their role in metabolic-immune crosstalk. The development of therapeutic strategies targeting exosomal lipid metabolism, such as exosome-based delivery systems for metabolic enzyme inhibitors, may potentially offer novel avenues in reversing immunosuppression and overcoming chemoresistance (103,104).

Addressing the aforementioned challenges will notably advance the application of exosomes in PC research and therapy. The development of more efficient, simpler and cost-effective techniques in isolating and extracting exosomes represents a key and urgent breakthrough warranted in the field. Simultaneously, establishing standardized protocols for exosome extraction is key to improving operational efficiency and minimizing sample loss. Furthermore, systematic comparative studies should be performed to clarify the advantages and suitable scenarios of exosomes over traditional nanocarriers such as liposomes in drug delivery. Lastly, active efforts are warranted to promote the translation of exosome-based therapies for PC from basic research to clinical trials.

In summary, exosomes hold notable potential as a therapeutic strategy for PC. Future research should focus on further understanding of their functional mechanisms, optimizing their isolation and extraction techniques and facilitating their

clinical translation, with the potential goal of offering novel treatment options for patients with PC in the clinic at the earliest opportunity.

6. Conclusions

Exosomes, as key mediators of intercellular communication, are involved in the occurrence and progression of PC. The present review systematically elaborated on the dual roles of exosomes in PC and analyzed their mechanisms of action at the molecular and signaling pathway levels. Previous research has identified that exosomes primarily promote the initiation and progression of PC through the following pathways: i) Directly regulating tumor cell behavior, driving the growth and proliferation of PC cells; ii) remodeling the immunosuppressive microenvironment, providing a more favorable environment for the growth and proliferation of PC cells; iii) inducing therapeutic resistance, thereby reducing the efficacy of drug treatments; and iv) regulating lipid metabolism, by reprogramming metabolism, affects the TME, thereby further supporting the progression of PC.

However, exosomes also exhibit potential in inhibiting the development of PC: i) Specific proteins, nucleic acids and other components carried by exosomes potentially offer novel avenues for the early diagnosis and prognosis assessment of PC; ii) certain exosomes can inhibit the progression of PC through different signaling pathways or by modulating the TME; iii) exosomes can serve as notable carriers for drugs effectively treating PC, enabling targeted delivery of therapeutic agents to achieve enhanced efficacy and reduced toxicity; and iv) the regulatory strategies based on the 'exosome-lipid metabolism-TME' axis may become a novel target for the treatment of PC.

The functional duality exhibited by exosomes in PC reflects their complex role in tumor biology: Exosomes can both promote malignant tumor progression and hold potential as diagnostic and therapeutic tools. This paradoxical characteristic suggests that their functions may be regulated by multiple factors, including the source cells, cargo composition and recipient microenvironment. Future research is warranted to further elucidate the specific mechanisms by which exosomes transmit information between different tumor stages and cell types and explore the molecular basis of their transformation from the 'dark side' to the 'bright side'.

In conclusion, a comprehensive understanding of the dual roles of exosomes in PC will not only help further the understanding of the communication network within the TME but also provide a notable basis in developing novel diagnostic strategies and therapeutic methods based on exosomes. Advancement in the clinical translation of exosomes may potentially open novel paths for the early detection and precision treatment of PC in the future.

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Authors' contributions

ZG contributed to the conception and overall design of the study, drafted the manuscript and prepared the figures and tables. QL reviewed and revised the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Competing interests

The authors declare that they have no competing interests.

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