Mesenchymal stem cell-derived exosomes: Regulators of progression and suppression in pancreatic cancer (Review)

HAOYAN ZHUANG[1] and XUEWEN SHI[2]

[1]Department of Anorectal, Weifang Hospital of Traditional Chinese Medicine, Weifang, Shandong 261000, P.R. China;
[2]Department of Anorectal, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan, Shandong 250000, P.R. China

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Abstract. Pancreatic cancer is a malignant digestive tract tumor with a poor prognosis. It remains one of the most challenging malignancies due to difficulties in early diagnosis and the development of chemotherapy resistance in advanced stages. Mesenchymal stem cells (MSCs), a distinct type of non-hematopoietic stem cells, play a crucial role in the tumor microenvironment owing to their unique tumor-homing capacity and immunomodulatory properties, which are largely mediated by their derived exosomes (EXOs). EXOs derived from MSCs can regulate the growth, invasion and metastasis of pancreatic cancer through the activation of specific signaling pathways. Furthermore, they have emerged as promising drug delivery vehicles and have demonstrated potential in anti-pancreatic cancer therapy. However, within the highly fibrotic tumor microenvironment of pancreatic cancer, the functions of MSC-derived EXOs are complex and dualistic, exhibiting both tumor-suppressive and tumor-promoting effects. Understanding the precise roles of MSC-derived EXOs in pancreatic cancer is essential for the development of effective therapeutic strategies. The present review systematically summarizes the dual regulatory mechanisms of MSC-derived EXOs in pancreatic cancer, elucidates the key molecules and signaling pathways involved, and discusses their clinical potential as novel therapeutic targets or drug delivery systems.

Contents

Correspondence to: Professor Xuewen Shi, Department of Anorectal, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, 42 Wenhua West Road, Lixia, Jinan, Shandong 250000, P.R. China
E-mail: shixuewenok@126.com

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1. Introduction

The incidence and mortality rates of pancreatic cancer (PC) have been steadily increasing; there were 441,000 cases of PC worldwide in 2017, compared with only 196,000 cases in 1990 (1). According to epidemiological data, PC has the lowest 5-year relative survival rate among all solid tumors, estimated at ~13% (2). Surgical resection combined with adjuvant chemotherapy represents the current standard of care and the most widely adopted clinical strategy for the treatment of PC (3). However, due to the asymptomatic nature of early-stage PC, the majority of patients are diagnosed at an advanced stage. Consequently, only a small subset of patients remains eligible for surgical intervention (4). Furthermore, the development of chemotherapy resistance, often resulting from prolonged treatment, notably impacts both the survival and quality of life of patients with PC. The pathogenesis of PC remains incompletely elucidated; however, in addition to modifiable risk factors such as smoking, alcohol consumption, obesity and diabetes, genetic mutations, familial inheritance and a complex tumor microenvironment (TME) are also recognized as critical contributing factors (1,5,6). The TME of PC is a complex ecosystem composed of cancer cells, stromal cells, immune cells and various extracellular components. PC cells actively drive genetic mutations; stromal cells produce abundant collagen and extracellular matrix leading to tissue fibrosis and highly expressed inflammatory factors create a pro-inflammatory environment. This unique TME establishes a robust foundation for the growth and metastasis of PC (7). Therefore, deepening the understanding of the molecular mechanisms underlying PC, developing more effective therapeutic strategies and overcoming chemotherapy resistance represent critical research directions that require further exploration.

Mesenchymal stem cells (MSCs) are multipotent stem cells characterized by high differentiation potential and strong

self-renewal capacity, which originate from the mesoderm and ectoderm during early development (8). Studies have indicated that MSCs actively participate in the progression of PC, including tumor growth and metastasis of cancer cells, as well as the modulation of TME (9-11). Studies have reported that MSCs can promote the progression of PC by secreting pro-tumorigenic factors (12) and differentiating into cancer-associated fibroblasts (CAFs) (13). However, other evidence suggests that MSCs can also suppress the development of PC. For example, Mohr *et al* (14) demonstrated that systemic MSC-mediated delivery of soluble tumor necrosis factor-related apoptosis inducing ligand, combined with X-linked inhibitor of apoptosis protein inhibition, could inhibit PC growth and metastasis. Additionally, IL-10-modified human MSCs were shown to inhibit PC progression by suppressing the secretion of pro-inflammatory cytokines IL-6 and TNF-α and inhibiting tumor angiogenesis (15). The role of MSCs in PC is closely associated with their derived EXOs (16).

EXOs are extracellular vesicles (EVs) with a diameter of 30-150 nm that are capable of transmitting complex information between cells (17), across distant tissues (18) and between tumor and stromal compartments (19). They originate from a wide variety of sources and are present in nearly all bodily fluids, and EXOs from different origins exhibit distinct functions (20). MSC-derived EXOs (MSC-EXOs) share numerous functional similarities with MSCs. However, compared with MSCs, MSC-EXOs demonstrate enhanced safety, superior penetrability, improved compatibility and higher stability when interacting with tumor cells (21,22). In recent years, the role of MSC-EXOs in the treatment of PC has been extensively investigated. For instance, it has been reported that human umbilical cord MSC-EXOs (hUC-MSC-EXOs) can promote the growth of pancreatic ductal adenocarcinoma by transferring microRNA (miR/miRNA)-100-5p into the PC tumor model (23). By contrast, Xie *et al* (24) reported opposing findings, demonstrating that hsa-miRNA-128-3p carried by hUC-MSC-EXOs suppressed the proliferation, invasion and migration of pancreatic ductal adenocarcinoma cells by targeting galectin-3. These findings indicate that MSC-EXOs serve a dual role in PC. The present article systematically elaborates on the dual tumor-promoting and tumor-suppressing mechanisms of MSC-EXOs in PC. It also clarifies the potential factors influencing this duality and provides direction for their application in targeted PC therapy.

2. MSCs and their derived EXOs

MSCs. The International Society for Cell Therapy has established the minimal defining criteria for MSCs: i) They must exhibit plastic-adherence under standard culture conditions; ii) they must express specific surface markers such as CD73, CD90 and CD105; iii) they must possess the capacity to differentiate into osteoblasts, chondrocytes and adipocytes *in vitro*; and iv) they must lack expression of CD14, CD34, CD45, CD11b, CD79a, CD19 and human leukocyte antigen-DR (25,26). MSCs can be isolated from a wide range of biological tissues, including bone marrow, adipose tissue, umbilical cord, placenta and peripheral blood (27-29). In previous years, MSCs have demonstrated notable potential in the treatment of PC; however, several limitations have also been identified. For example, studies have indicated that MSCs may increase the risk of tumorigenicity and cell death (30,31). To address these concerns, researchers have proposed using MSC-EXOs as an alternative therapeutic approach for PC. These EXOs exhibit a number of functions similar to those of MSCs, offer improved safety and stability profiles and can serve as excellent carriers for delivering antitumor drugs (32).

MSC-EXOs. EXOs are nanoscale EVs enclosed by a double-layer lipid membrane (33), which are widely derived from various cell types, such as cancer cells, immune cells, stem cells and even food or plant cells. The biogenesis and synthesis of EXOs involve a complex process (Fig. 1). Initially, their formation begins with the invagination of the cell membrane, where ubiquitination of surface receptors initiates the endocytic process, leading to the formation of early endosomes. Over time, early endosomes mature into late endosomes, within which multiple intraluminal vesicles (ILVs) are formed through inward budding; the entire structure is referred to as a multivesicular body (MVB) (34,35). MVBs primarily face two fates: One is fusion with lysosomes resulting in degradation of their contents, and the other is fusion with the plasma membrane, through which ILVs are released into the extracellular environment as EXOs via exocytosis (36). This process involves various key molecules, including Rab GTPase proteins; endosomal sorting complexes required for transport, tetraspanins and ceramide (37-40). EXOs carry a diverse range of bioactive molecules. Their protein cargo includes heat shock proteins (HSP70, HSP90), GTPases, tetraspanins (CD63, CD81, CD9, CD82), as well as various transport, fusion and adhesion molecules (41-43). Additionally, EXOs contain lipids such as cholesterol, sphingomyelin, glycosphingolipids, phosphatidylcholine, phosphatidylserine and ceramides (44), along with various nucleic acids such as mRNA, miRNA, circular (circ)RNA, long non-coding (lnc)RNA and small nuclear (sn)RNA (45).

3. MSC-EXOs promote the progression of PC

The tumor-promoting role of MSC-EXOs in PC has been demonstrated in multiple studies (23,46,47). For instance, B-MSC-EXOs, AD-MSC-EXOs and UC-MSC-EXOs can jointly exert cancer-promoting effects through different mechanisms of action (Fig. 2). The current section will focus on elucidating the specific molecular mechanisms and signaling pathways underlying their pro-tumorigenic effects, including promoting tumor cell proliferation, shaping an immunosuppressive microenvironment and mediating chemotherapy resistance (Table I). By systematically elaborating these mechanisms, the present study aimed to provide researchers with a clear understanding of the tumor-promoting functions of MSC-EXOs in PC and establish a theoretical foundation for developing future exosome-targeted therapeutic strategies.

MSC-EXOs promote the proliferation of tumor cells. MSC-EXOs can directly promote the proliferation of PC cells, thereby exerting tumor-promoting effects. In the study by Ding *et al* (23), hUC-MSC-EXOs carrying miR-100-5p were demonstrated to promote the proliferation of PC cells PANC1 and BxPC3 in both *in vivo* and *in vitro* studies, consequently

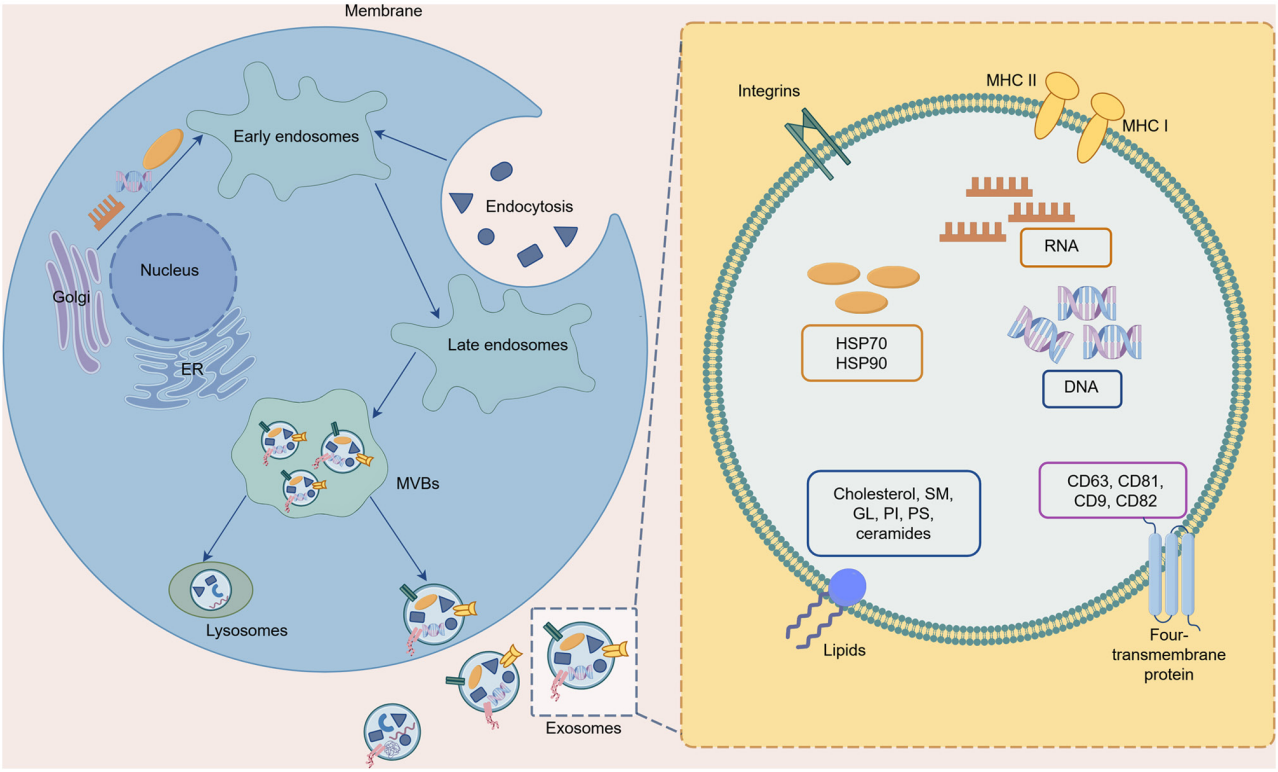

Figure 1. Biogenesis and synthesis of exosomes. The figure was generated using Figdraw (www.figdraw.com). MVBs, multivesicular bodies; SM, sphingomyelin; GL, glycosphingolipids; PL, phosphatidylcholine; PS, phosphatidylserine; EXOs, exosomes; MHC, major histocompatibility complex; HSP, heat shock proteins.

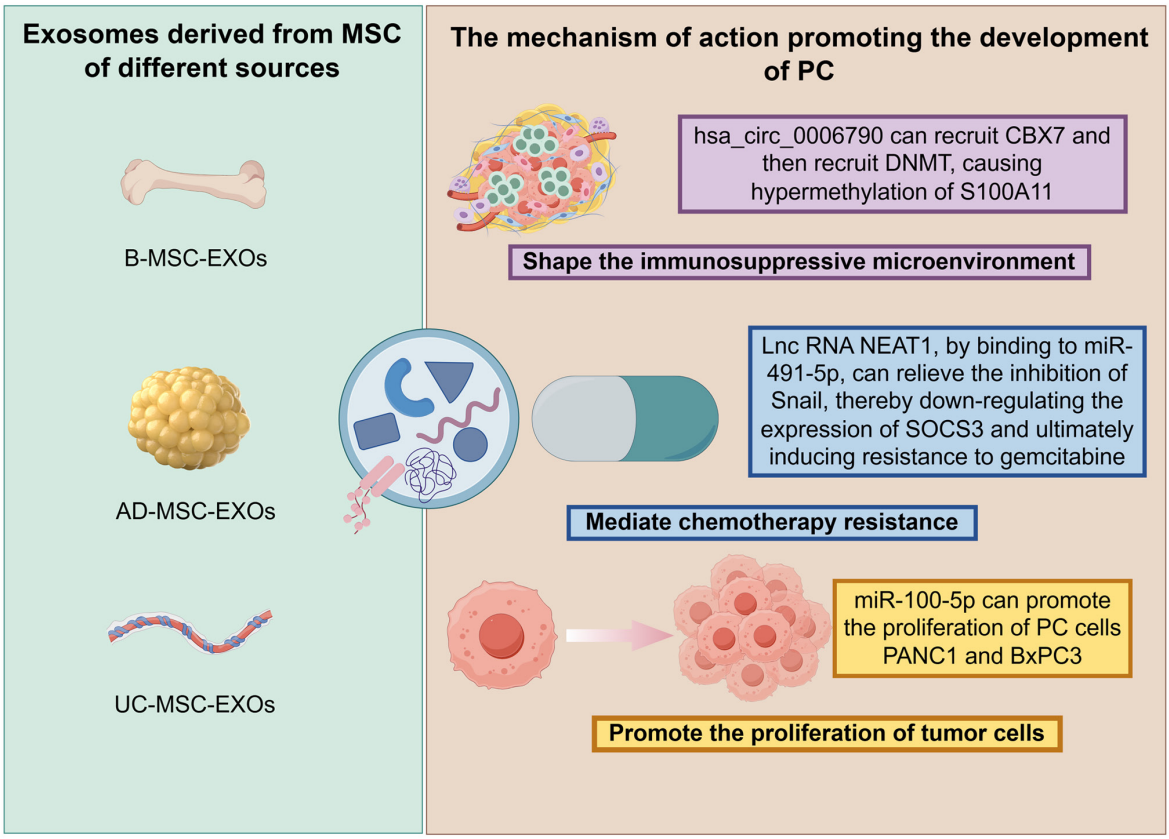

Figure 2. MSC-EXOs of different sources promote the progression of PC. The figure was generated using Figdraw (www.figdraw.com). EXOs, exosomes; MSCs, mesenchymal stem cells; B-MSC-EXOs, bone marrow mesenchymal stem cell-derived exosomes; AD-MSC-EXOs, adipose mesenchymal stem cell-derived exosomes; UC-MSC-EXOs, umbilical cord mesenchymal stem cell-derived exosomes; PC, pancreatic cancer; SOCS3, suppressor of cytokine signaling 3; CBX7, chromobox protein homolog 7; DNMT, DNA methyltransferase; miR, microRNA.

Table I. A summary of the research on the promoting role of MSCs-EXOs from different sources in PC.

First author, year	Source of exosomes	Key cargos	Specific mechanisms	Results	(Refs.)
Ding *et al*, 2021	UC-MSCs-EXOs	miR-100-5p	Promote the proliferation of PC cells PANC1 and BxPC3	Promote the growth of pancreatic ductal adenocarcinoma	(23)
Gao *et al*, 2022	B-MSCs-EXOs	hsa_circ_0006790	Recruit CBX7 and DNMT, causing hypermethylation of the downstream target gene S100A11, resulting in a downregulation of its expression levels	Promote immune escape in PC cells	(46)
Wu *et al*, 2023	AD-MSCs-EXOs	lncRNA NEAT1	Competitively bind to miR-491-5p, relieve the inhibition of the transcription factor Snail, thereby downregulating the expression of SOCS3	Induce resistance to gemcitabine	(47)

MSCs, mesenchymal stem cells; EXOs, exosomes; UC-MSCs-EXOs, EXOs derived from umbilical cord MSCs; B-MSCs-EXOs, EXOs derived from bone marrow MSCs; AD-MSCs-EXOs, EXOs derived from adipose MSCs; DNMT, DNA methyltransferase; PC, pancreatic cancer; SOCS3, suppressor of cytokine signaling 3; miR, microRNA; circ, circular RNA; lncRNA, long non-coding RNA; CBX7, chromobox protein homolog 7.

accelerating the growth of pancreatic ductal adenocarcinoma. This finding not only reveals the key mechanism by which hUC-MSC-EXOs contribute to the development and progression of pancreatic ductal adenocarcinoma through the transfer of miR-100-5p, but also provides new insights for targeted intervention. Inhibiting miR-100-5p may represent a potential therapeutic strategy to block EXO-mediated pro-tumorigenic effects, thereby opening new avenues for precision therapy in pancreatic ductal adenocarcinoma.

MSC-EXOs shape the immunosuppressive microenvironment. MSC-EXOs can participate in shaping the immunosuppressive microenvironment of PC through complex mechanisms, thereby providing favorable conditions for tumor initiation and progression. For example, Gao *et al* (46) found that bone marrow MSC-EXOs (B-MSC-EXOs) carrying hsa_circ_0006790 can recruit chromobox protein homolog 7, which subsequently recruits DNA methyltransferases, leading to hypermethylation of the promoter region of the downstream target gene S100A11 and resulting in its downregulation. As a key molecule involved in immunoregulation, the decreased expression of S100A11 ultimately induces immune escape in PC cells. This study by Gao *et al* (46) not only reveals the specific mechanism by which B-MSC-EXOs contribute to the formation of the immunosuppressive microenvironment in PC but also provides a potential target for developing novel immunotherapy strategies targeting the exosomal signaling axis.

MSC-EXOs mediate chemotherapy resistance. MSC-EXOs can participate in mediating chemotherapy resistance in PC. For example, a study showed that human adipose MSC-EXOs (hAD-MSC-EXOs) are enriched with the lncRNA NEAT1, which can competitively bind to miR-491-5p, thereby relieving its inhibition of the transcription factor Snail. This subsequently leads to downregulation of suppressor of cytokine signaling 3 (SOCS3) expression, ultimately inducing resistance to gemcitabine in PC cells (47). This mechanism highlights the critical role of exosome-carried lncRNA in mediating chemotherapy resistance, not only providing a new molecular perspective for understanding drug resistance in PC but also offering potential therapeutic strategies for reversing resistance, such as targeting the NEAT1/miR-491-5p/Snail/SOCS3 signaling axis to reduce chemoresistance.

In conclusion, although MSC-EXOs derived from different tissues such as umbilical cord, bone marrow and adipose can promote the progression of PC through multiple mechanisms, related research is still relatively limited, and more experimental evidence is needed to verify the specific cancer-promoting mechanisms. In addition, apart from gemcitabine, there are currently numerous drugs used to inhibit the development of PC. Therefore, whether hAD-MSC-EXOs still exhibit cancer-promoting effects when used in conjuction with other anticancer drugs remains to be elucidated. In addition, whether MSC-EXOs derived from the same tissue only serve a promoting role in PC also remains to be elucidated. Through in-depth sorting and analysis, a more complex fact has been demonstrated: Even MSC-EXOs derived from the same tissue exhibit a dual role in PC and may either promote tumor development or inhibit its progression.

4. Therapeutic potential of MSC-EXOs in PC

Although MSC-EXOs can promote the initiation and progression of PC through various mechanisms, current research focuses more on their tumor-suppressive roles. For instance, UC-MSC-EXOs, B-MSC-EXOs, hA-MSC-EXOs, hAF-MSC-EXOs and Dental-MSC-EXOs can jointly exert anti-cancer effects through different mechanisms of action

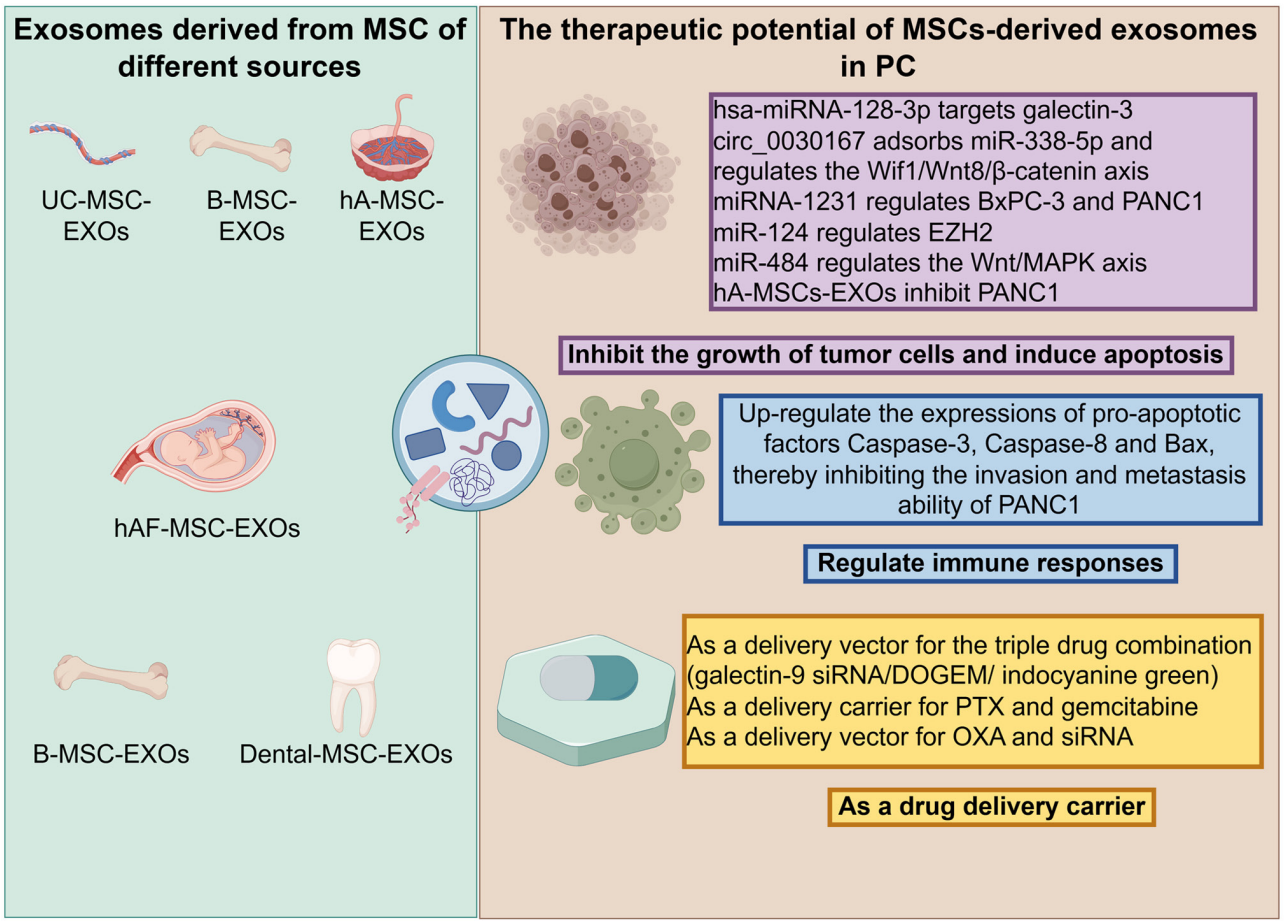

Figure 3. Therapeutic effect of MSC-EXOs of different sources in PC. The figure was generated using Figdraw (www.figdraw.com). EXOs, exosomes; UC-MSC-EXOs, umbilical cord mesenchymal stem cell-derived exosomes; B-MSC-EXOs, bone marrow mesenchymal stem cell-derived exosomes; hA-MSC-EXOs, human amniotic mesenchymal stem cell-derived exosomes; hAF-MSC-EXOs, human amniotic fluid mesenchymal stem cell-derived exosomes; Dental-MSC-EXOs, dental pulp mesenchymal stem cell-derived exosomes; PTX, paclitaxel; OXA, oxaliplatin; PC, pancreatic cancer; miR, microRNA; DOGEM, dodecyloxybenzyl gemcitabine; si, small interfering.

(Fig. 3). In fact, owing to their notable immunomodulatory capabilities and tumor-homing properties, MSC-EXOs exhibit multifaceted functions in tumor suppression: On the one hand, they can directly inhibit the proliferation of PC cells and induce apoptosis; on the other hand, they can indirectly exert anti-tumor effects by modulating immune responses. Furthermore, due to their high biocompatibility, low immunogenicity and efficient targeted delivery capacity, MSC-EXOs serve as a highly promising drug delivery system and are widely used for loading antitumor agents, thereby further enhancing their value in suppressing PC (Table II) (48,49). Therefore, despite reports indicating that MSC-EXOs may promote the growth and development of PC, their functions in tumor suppression remain more comprehensive and hold greater translational potential.

MSC-EXOs inhibit the growth of tumor cells and induce apoptosis. MSC-EXOs exert notable tumor-suppressive effects by inhibiting tumor cell growth and inducing apoptosis. Multiple studies support this conclusion through various mechanisms. For instance, hsa-miRNA-128-3p in hUC-MSC-EXOs can effectively inhibit the proliferation, invasion and migration of PC PANC1 cells by targeting galectin-3 (24). Meanwhile, circ_0030167 from human (h)B-MSC-EXOs suppresses the proliferation, invasion and metastasis of PC cells by sponging miR-338-5p and regulating the Wnt inhibitory factor 1/Wnt8/β-catenin axis (50). Additionally, miRNA-1231 from B-MSC-EXOs negatively regulates the proliferation, migration, invasion and matrix adhesion of both BxPC-3 and PANC1 cells (51). Xu *et al* (52) demonstrated that B-MSC-EXOs carrying miR-124 inhibit proliferation, invasion and metastasis, while promoting apoptosis in AsPC1 and PANC1 cells by modulating enhancer of zeste homolog 2 expression. Another study indicated that miR-484, carried by hB-MSC-EXOs, suppresses proliferation and migration and induces apoptosis in PC cells via regulation of the Wnt/MAPK axis (53). Furthermore, human amniotic MSC-EXOs inhibit the proliferation of PANC1 cells by downregulating the expression of Sugen kinase 269, E-cadherin, vimentin and the Snail transcription factor (54), a finding further supported by studies from Safari and Dadvar (55) and Safari *et al* (56). Collectively, these findings demonstrate that MSC-EXOs inhibit PC cell proliferation and promote apoptosis through multiple molecular mechanisms, serving a crucial role in suppressing PC progression.

MSC-EXOs regulate immune responses. MSC-EXOs can exert antitumor effects by modulating immune responses. For

Table II. A summary of research on the therapeutic potential of MSCs-EXOs of different sources in PC.

First author, year	Source of exosomes	Key cargos	Specific mechanism	Result	(Refs.)
Chen *et al*, 2022	hAF-MSCs-EXOs	hAF-MSCs-EXOs	Upregulate the expression of pro-apoptotic factors caspase-3, caspase-8 and Bax	Inhibit the invasion and metastasis ability of PC cell line PANC1	(9)
Xie *et al*, 2022	UC-MSCs-EXOs	hsa-miR-128-3p	Target galectin-3	Inhibit the proliferation, invasion and migration of PC cell line PANC1	(24)
Zhang *et al*, 2025	B-MSCs-EXOs	B-MSCs-EXOs	As a delivery vector for the triple drug combination (galectin-9 siRNA/DOGEM/indocyanine green)	Notably enhance the anti-PC effect	(48)
Zhou *et al*, 2020	B-MSCs-EXOs	B-MSCs-EXOs	As a delivery vector for PTX and gemcitabine	Effectively overcome chemotherapy resistance in PC	(49)
Yao *et al*, 2021	B-MSCs-EXOs	circ_0030167	Adsorb miR-338-5p and regulate the Wif1/Wnt8/β-catenin axis	Inhibit the proliferation, invasion and metastasis of PC cells	(50)
Shang *et al*, 2019	B-MSCs-EXOs	miR-1231	Directly regulate and inhibit the proliferation, migration and invasion of PC cell lines BxPC-3 and PANC1	Inhibit the occurrence and progression of PC	(51)
Xu *et al*, 2020	B-MSCs-EXOs	miR-124	Regulate the expression of EZH2	Inhibit the proliferation, metastasis and invasion of AsPC1 and PANC1, and promote their apoptosis	(52)
Lin *et al*, 2023	B-MSCs-EXOs	miR-484	Regulate the Wnt/MAPK axis	Inhibit the proliferation, invasion and metastasis of PC cells	(53)
Alidoust *et al*, 2022	hA-MSCs-EXOs	hA-MSCs-EXOs	Downregulate the expression of SgK269, E-cadherin, vimentin and Snail transcription factors	Inhibit the proliferation of PANC1 cells	(54)
Zhou *et al*, 2021	B-MSCs-EXOs	B-MSCs-EXOs	Simultaneously loaded with OXA and siRNA	Inhibit the polarization of tumor-associated macrophages, promote the recruitment of cytotoxic T lymphocytes and downregulate the activity of Treg cells	(57)
Klimova *et al*, 2023	Dental-MSCs-EXOs	Dental-MSCs-EXOs	As a delivery carrier for gemcitabine	Inhibit the proliferation, invasion and metastasis of PC cells	(58)

MSCs, mesenchymal stem cells; EXOs, exosomes; UC-MSCs-EXOs, EXOs derived from umbilical cord MSCs; B-MSCs-EXOs, EXOs derived from bone marrow MSCs; hA-MSCs-EXOs, EXOs derived from human amniotic MSCs; hAF-MSCs-EXOs, EXOs derived from human amniotic fluid MSCs; dental-MSCs-EXOs, EXOs derived from dental pulp MSCs; PTX, paclitaxel; OXA, oxaliplatin; PC, pancreatic cancer; SgK269, Sugen kinase 269; EZH2, enhancer of zeste homolog 2; miR, microRNA; circ, circular RNA; Treg, regulatory T cell; siRNA, small interfering RNA.

example, a study by Chen *et al* (9) demonstrated that human amniotic fluid MSC-EXOs (hAF-MSC-EXOs) markedly upregulate the expression of pro-apoptotic factors caspase-3, caspase-8 and Bax, thereby inhibiting the invasion and

metastatic capabilities of PANC1 cells. This finding suggests that hAF-MSC-EXOs may enhance immune effector mechanisms by upregulating pro-apoptotic factors, consequently suppressing the progression of PC.

MSC-EXOs as a drug delivery carrier. MSC-EXOs are regarded as a highly promising drug delivery vehicle for anti-PC therapy due to their excellent biocompatibility, low immunogenicity and inherent targeting capability. A study has shown that B-MSC-EXOs can serve as carriers for a triple-drug combination [galectin-9 small interfering (si)RNA/dodecyloxybenzyl gemcitabine/indocyanine green], demonstrating favorable tumor-targeting ability and pH-responsive release characteristics both *in vivo* and *in vitro*, notably enhancing the anti-PC efficacy (48). Furthermore, B-MSC-EXOs, as delivery vehicles for paclitaxel and gemcitabine, effectively overcome chemotherapy resistance in PC owing to their superior homing and penetration capabilities during delivery (49). Zhou *et al* (57) developed a dual-delivery biosystem using B-MSC-EXOs capable of co-loading oxaliplatin and siRNA. This system not only elicits an antitumor immune response by inhibiting tumor-associated macrophage polarization, promoting T lymphocyte recruitment and downregulating regulatory T cell activity, but also exhibits higher stability and lower side effects compared with conventional synthetic carriers. An *in vitro* study by Klimova *et al* (58) found that EXOs derived from human dental pulp MSCs can act as carriers for gemcitabine, significantly inhibiting the growth of PC cells. In summary, the multiple advantages demonstrated by MSC-EXOs in drug delivery indicate their potential as an efficient and safe nanoscale platform for the treatment of PC.

5. EXOs derived from engineered MSCs

Over time, genetic engineering has evolved into a pivotal approach for treating various diseases, including hematological disorders, genetic conditions, and cancers (59-61). Particularly in the field of oncology, continuous technological advancements and expanding applications have notably enhanced the efficacy and safety of genetic engineering-based therapies, demonstrating broad prospects for clinical application. MSC-EXOs have garnered considerable attention in the treatment of PC due to their unique biocompatibility, low immunogenicity and targeted delivery capabilities. However, natural EXOs face limitations such as insufficient targeting specificity, limited efficacy of their cargo and rapid clearance, which substantially restrict their clinical translation and therapeutic effectiveness. Consequently, combining them with genetic engineering strategies can markedly enhance their tumor-targeting ability, treatment specificity and immunomodulatory functions in PC.

PC CAFs serve a critical role in the initiation and progression of PC. Targeted reprogramming of CAFs may represent a promising therapeutic strategy for PC. Zhou *et al* (62) employed a genetic engineering approach to endogenously modify B-MSC-EXOs, enabling surface display of integrin α5 targeting peptides and concomitant overexpression of miR-148a-3p, thereby achieving precise reprogramming of CAFs and providing new insights for clinical translation of this strategy. On the other hand, Buocikova *et al* (63) genetically engineered EXOs from placental MSCs to express the yeast cytosine deaminase::uracil phosphoribosyltransferase fusion enzyme. In a model of pancreatic ductal adenocarcinoma, this approach demonstrated potent cytotoxicity-reducing effects. Therefore, it offers a promising cell-free therapeutic strategy for PC. Although genetically engineered MSC-EXOs are considered a promising strategy for cancer treatment, their current application in PC remains in its early stages and requires further in-depth research to advance their development. The development of more efficient and safer engineered exosome-based therapeutic strategies remains a notable challenge in the current treatment of PC.

6. Possible factors for MSCs serving a dual role in PC

MSC-EXOs exhibit a dual role in PC, a phenomenon that warrants in-depth consideration. The underlying mechanisms are likely closely associated with the following factors. Firstly, the functional properties of EXOs are notably influenced by their cellular origin. Although EXOs derived from different sources of MSCs share common characteristics, such as high self-renewal capacity, multipotent differentiation potential, immunomodulatory activity, pro-angiogenic effects and tumor-homing ability (64-74) (Fig. 4), the specific molecules present on their surface and their cargo compositions may vary considerably, potentially leading to distinct functional orientations (75-79) (Table III). MSC-EXOs from different tissue sources have demonstrated a dual role in PC, which has been discussed in the present review. On the other hand, the stage of PC progression may also affect the functional outcomes of EXOs. For instance, early-stage PC may respond more favorably to therapy with MSC-EXOs compared with advanced-stage disease; however, this hypothesis still lacks robust experimental evidence and thus represents a critical question that urgently requires validation in future research. In addition, the differences in experimental design within this research field are another reason for the contradictions among different research results. Specifically, the differences in the extraction and identification methods of EXOs, cell co-culture systems and animal models (such as mouse strains, quantities and tumor-bearing sites) may all introduce notable heterogeneity, thereby affecting the comparability and repeatability of research conclusions.

7. Challenges and future prospects

In summary, MSC-EXOs exhibit a notable dual role in PC. The present review has systematically discussed their specific molecular mechanisms and functional characteristics in PC, and summarized the latest research advances in engineered modification of MSC-EXOs. In-depth elucidation of the key molecules, proteins and signaling pathways involved will provide new research directions and intervention strategies for the treatment of PC.

Despite the considerable tumor-suppressive potential of MSC-EXOs in PC, several unresolved issues and challenges remain. First, the techniques for isolating and extracting MSC-EXOs are still inadequate. Although multiple methods have been developed for exosome isolation and extraction, such as ultracentrifugation (80,81), ultrafiltration (82-84), flushing separation (85), precipitation (86-88), immunoaffinity

Table III. Functional emphasis of MSCs from different sources.

First author, year	Advantage	Source of EXOs	Result	(Refs.)
Tracy *et al*, 2019	Output	hAF-MSC-EXOs compared with hB-MSC-EXOs	hAF-MSC-EXOs have a higher yield	(75)
Wang *et al*, 20220	Tissue repair ability	hUC-MSC-EXOs compared with hB-MSC-EXOs and hAD-MSC-EXOs	hUC-MSC-EXOs have an advantage in tissue repair ability	(76)
Ji *et al*, 2019	Immunomodulatory activity	Human dental-MSC-EXOs compared with hB-MSC-EXOs	Human dental-MSC-EXOs have an advantage in immunomodulatory activity	(77)
Katsuda *et al*, 2013	Neurolysin activity	hAD-MSC-EXOs compared with hB-MSC-EXOs	hAD-MSC-EXOs have higher neurolysin activity	(78)
Pomatto *et al*, 2021	Angiogenesis ability	hAD-MSC-EXOs compared with hB-MSC-EXOs	hAD-MSC-EXOs have higher angiogenesis ability	(79)

MSC, mesenchymal stem cell; EXOs, exosomes; hAF-MSC-EXOs, human amniotic fluid -derived EXOs; hB-MSC-EXOs, human bone marrow MSC-derived EXOs; hUC-MSC-EXOs, human umbilical cord MSC-derived EXOs; hAD-MSC-EXOs, adipose MSC-derived EXOs; dental-MSC-EXOs, human dental pulp MSC-derived EXOs.

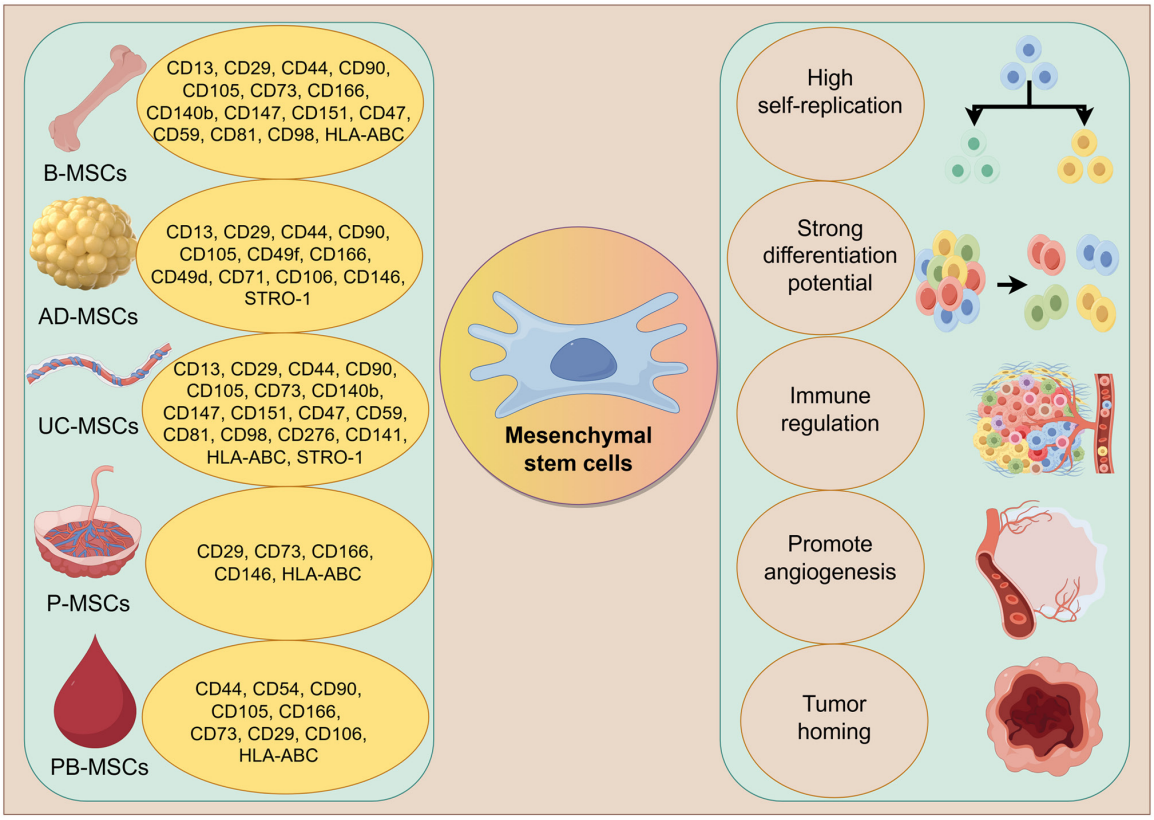

Figure 4. Surface molecules and common functions of mesenchymal stem cells from different sources. The molecules and inclusions carried on the surface of MSC-EXOs from different sources vary, but they generally possess common capabilities such as high self-replication, strong differentiation potential, immune regulation, promote angiogenesis and tumor homing ability. B-MSCs (64), AD-MSCs (65-69), UC-MSCs (64), P-MSCs (70-72), PB-MSCs (73,74). The figure was generated using Figdraw (www.figdraw.com). B-MSCs, bone marrow-derived mesenchymal stem cells; AD-MSCs, adipose-derived mesenchymal stem cells; UC-MSCs, umbilical cord-derived mesenchymal stem cells; P-MSCs, placenta-derived mesenchymal stem cells; PB-MSCs, peripheral blood derived mesenchymal stem cells.

capture (89-91), microfluidics (92-95) and mass spectrometry (96), each of these approaches has its own limitations. There is currently a lack of a simple, efficient, cost-effective and standardized extraction protocol suitable for clinical application. Second, research on and preparation of MSC-EXOs lack unified standards. No authoritative institutions have yet

established clear guidelines for their isolation, preparation, characterization and functional evaluation. Third, large-scale production, storage and transportation systems remain underdeveloped. Systematic research and solutions are still needed regarding large-scale preparation, long-term stable storage methods and potential loss of activity and integrity during transportation. Fourth, evidence for clinical translation is insufficient. Most current studies are limited to animal experiments; future research should focus on clinical trials to validate the safety and efficacy of these EXOs in human applications. Fifth, the immunogenicity risks brought about by the engineering modification of MSC-EXOs need to be systematically evaluated. For example, whether the natural low immunogenicity advantage of MSC-EXOs will be altered after engineering. Or, whether it may trigger an immune response in the body, especially in the context of repeated administration for PC, which would be a core issue regarding treatment safety. Sixth, the dense fibrotic matrix of PC may severely impede the penetration ability of EXOs, and their pharmacokinetic performance in this environment requires further research and confirmation. Finally, there is a lack of horizontal efficacy comparisons among various treatment methods for PC. For instance, compared with traditional nanoparticles (such as liposomes) that have entered clinical application, MSC-EXOs may have inherent advantages in active targeting and biocompatibility, but they are slightly inferior in drug loading capacity and the maturity of production processes (97). However, future research should prospectively explore strategies for combining the two to achieve synergistic therapeutic effects.

Although the present article systematically expounds the research progress of MSC-EXOs in PC, there are still certain limitations. Firstly, due to the rapid development of research in this field, this article may not be able to cover all the latest released research achievements. Secondly, the discussion on the mechanism of MSC-EXOs in promoting cancer still needs to be further clarified. In addition, the analysis of the potential and challenges of EXOs derived from engineered MSCs in this field needs to be strengthened. Looking to the future, first of all, researchers should focus on developing a simple, efficient and low-cost standardized extraction scheme for the separation and extraction of EXOs. Secondly, more in-depth exploration and research should be performed on the role of MSC-EXOs in PC to address the potential loss issues that may arise during their large-scale production, storage and transportation. In addition, a systematic safety assessment of the immunogenicity risk and *in vivo* pharmacokinetic behavior of engineered modified EXOs is necessary, which is a prerequisite for their clinical transformation. Another important task lies in performing a horizontal efficacy comparison between exosome therapy and other treatment methods, with the aim of providing the optimal treatment strategy for patients with PC. Finally, accelerating the transformation of MSC-EXOs from basic research to clinical practice makes it possible for them to become an important component of the comprehensive treatment system for PC.

8. Conclusion

MSC-EXOs serve as highly plastic messengers in PC, where their role in promoting or suppressing tumor progression is not fixed but rather determined by their specific surface molecules and cargo contents, which are closely associated with the diverse origins of MSCs. Future research should focus on transforming MSC-EXOs from a 'double-edged sword' into a precise weapon against PC. The primary task is to deeply explore its specific active ingredients and their precise regulatory mechanisms in PC and, on this basis, strategies for engineering and modifying MSC-EXOs should be established. At the same time, establishing standardized, repeatable, low-cost yet high-purity separation and purification technologies is the core step for it to move towards clinical application. In addition, it is important to actively explore the combined application of EXOs therapy and existing treatment methods. Only through in-depth exploration at multiple levels can this promising treatment method be advanced from the laboratory to clinical practice, bringing new treatment options for patients with PC.

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Authors' contributions

HZ contributed to the conception and overall design of the study. HZ drafted the manuscript and prepared the figures and tables. XS reviewed and revised the manuscript. All authors read and approved the final version of the manuscript. Data authentication was not applicable.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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