Regenerative Therapy 29 (2025) 202–216

Contents lists available at ScienceDirect

Regenerative Therapy

journal homepage: http://www.elsevier.com/locate/reth

Review

Exosome-based approaches in cancer along with unlocking new insights into regeneration of cancer-prone tissues

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ARTICLE INFO

Article history:
Received 9 February 2025
Received in revised form
1 March 2025
Accepted 18 March 2025

Keywords:
Cancer
Exosome
Drug delivery
Diagnosis
Exosomal microRNAs
Tumor microenvironment
Tissue regeneration

ABSTRACT

Most eukaryotic cells secrete extracellular vesicles called exosomes, which are involved in intercellular communication. Exosomes play a role in tumor development and metastasis by transporting bioactive chemicals from cancerous cells to other cells in local and distant microenvironments. However, the potential of exosomes can be used by engineering them and considering different therapeutic approaches to overcome tumors. Exosomes are a promising drug delivery approach that can help decrease side effects from traditional treatments like radiation and chemotherapy by acting as targeted agents at the tumor site. The present review provides an overview of exosomes and various aspects of the role of exosomes in cancer development, which include these items: exosomes in cancer diagnosis, exosomes and drug delivery, exosomes and drug resistance, exosomal microRNAs and exosomes in tumor microenvironment, etc. Cancer stem cells release exosomes that nurture tumors, promoting unwanted growth and regeneration, and these types of exosomes should be inhibited. Ironically, exosomes from other cells, such as hepatocytes or mesenchymal stem cells (MSCs), are vital for healing organs like the liver and repairing gastric ulcers. Without proper treatment, this healing process can backfire, potentially leading to disease progression or even cancer. What can be found from various studies about the role of exosomes in the field of cancer is that exosomes act like a double-edged sword; on the other hand, natural exosomes in the body may play an important role in the process and progression of cancer, but by engineering exosomes, they can be directed towards target therapy and targeted delivery of drugs to tumor cells. By examining the role and application of exosomes in various mechanisms of cancer, it is possible to help treat this disease more efficiently and quickly in preclinical and clinical research.

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Peer review under responsibility of the Japanese Society for Regenerative Medicine.

https://doi.org/10.1016/j.reth.2025.03.005

1. Introduction

Exosomes are among the family of extracellular vesicles. Extracellular vesicles are classified according to their size and origin. Exosomes are the smallest members of this family and are made through endocytosis. Several molecules are involved in their production, intracellular transport and secretion. Several mechanisms have been identified in their construction and loading [1]. Exosomes, which range in size from 40 to 160 nm, have a two-layer membrane structure secreted by various cells and can be found in body fluids such as blood, urine, and breast milk [2–4]. These nanoparticles participate in many vital cellular processes, including intercellular communication, immune regulation, tissue healing, and disease progression and also act as carriers of various compounds such as DNA, RNA, proteins, lipids, and other bioactive components and after being released into the extracellular environment, they reach the target cells (Fig. 1). Because these vesicles contain biological molecules, after reaching the target cells, they cause changes in the fate and function of those cells. Consequently, exosomes play an important role in facilitating information transfer and regulating physiological and pathological cellular processes [2,5,6]. Researchers believe exosomes can be used in medical fields such as biomarkers, biocarriers and gene therapy [7].

In the field of cancer, exosomes from cancer cells contribute to immune modulation by transferring immunosuppressive molecules and influencing the activity of immune cells. These exosomes can inhibit the activity of NK cells and T cells, stimulate the proliferation of myeloid-derived suppressor cells (MDSC), and change the phenotype of immune cells, helping the immune system evade the tumor [8,9]. In addition, they can also facilitate cancer progression and metastasis by promoting angiogenesis [10]. Despite their involvement in tumor progression and metastasis, exosomes derived from healthy and diseased cells can be used as carriers for drug delivery [11,12]. Today, the key role of exosomes in the medical field has been highlighted; the distinct advantages of exosomes include high biocompatibility and cellular uptake, low toxicity, long half-life in the circulatory system, intrinsic ability to target specific tissues, and the ability to cross barriers such as the blood-brain barrier, makes them an attractive option for targeted drug delivery [3,13,14]. Exosomes prepared from non-tumor or non-human sources such as bacteria [15], milk [16,17] and plants [18–20] have been considered promising drug carriers due to their low toxicity and easy access [21]. In cancer treatment, exosomes can act as nanocarriers for antitumor drugs, gene-based drugs, and other nanomaterials with anticancer capabilities [22]. They can increase the effectiveness of chemotherapy drugs, prevent cancer growth and induce apoptosis in cancer cells [23,24]. The ability of exosomes to carry hydrophobic and hydrophilic molecules, effective homing in the tumor site, and crossing the blood-brain barrier make them promising tools for tumor treatment, including brain tumors [25–27]. In addition to drug delivery, exosomes also help cancer immunotherapy. Exosomes from antigen-presenting cells, such as dendritic cells (DCs), can help fight cancer by stimulating immune responses [28]. Immature exosomes derived from DCs can treat melanoma and non-small cell lung cancer (NSCLC) [29–31]. However, despite their great potential, the clinical implementation of exosomes as drug delivery systems is still at an early stage due to challenges in isolation, identification, quality control, and standardization [22,32,33]. Some researchers reported the relationship between exosomes and the promotion and development of various cancer types (Table 1).

In a short comparison of exosomes and liposomes, it is understood that one of the most effective therapeutic nanocarriers is the liposome; despite their great encapsulation efficiency and ability to be made at scale for commercial purposes, liposomes are often criticized for their weak intracellular drug delivery and short blood circulation and need to be optimized [34–39]. On the other hand, exosomes have been extensively explored as delivery vehicles due to low immunogenicity, efficient cargo delivery, and possibly intrinsic homing capacity. However, the therapeutic application of exosomes should be further investigated due to the structural complexity and lack of efficient isolation and drug-loading techniques [40,41].

In this review, various aspects of the role of exosomes in cancer development will be mentioned, which include these items: exosomes and cancer diagnosis, exosomes and drug delivery, exosomes and drug resistance, exosomal microRNAs and exosomes in tumor microenvironment, etc. Exosomes produced by Cancer stem cells can maintain a stable environment within tumors and promote self-renewal, leading to undesirable repair and regeneration of tumor tissues; these types of exosomes should be inhibited, while hepatocyte- and MSC-derived exosomes are crucial for the regeneration and repair of some tissues, such as the liver and gastric ulcers, as lack of proper treatment may lead to disease progression and cancer.

2. Exosomes and drug delivery system in cancer

Researchers are interested in exosomes as novel therapeutic carriers for cancer treatment. These naturally occurring nanoparticles can transport nucleotides, macromolecules, and tiny chemicals to cure cancer [31,33]. Lung, ovarian, and breast cancer cells have all been successfully targeted and killed by exosomes loaded with anticancer small molecules like paclitaxel (PTX) [61–64]. Gemcitabine-containing exosomes markedly boosted animal survival and inhibited tumor development in mice with pancreatic cancers, and at the same time, there was less harm to good tissues [65]. In clinical studies, exosomes produced from dendritic cells have demonstrated considerable promise in triggering anticancer immune responses and targeted cell death of tumor cells. These exosomes can selectively target and eliminate tumor cells, prompting the immune system to attack the tumor [66–68]. However, a notable limitation is the inadequate efficacy of drug loading in exosomes; additional investigation is required to enhance the effectiveness of these loading techniques (Fig. 2).

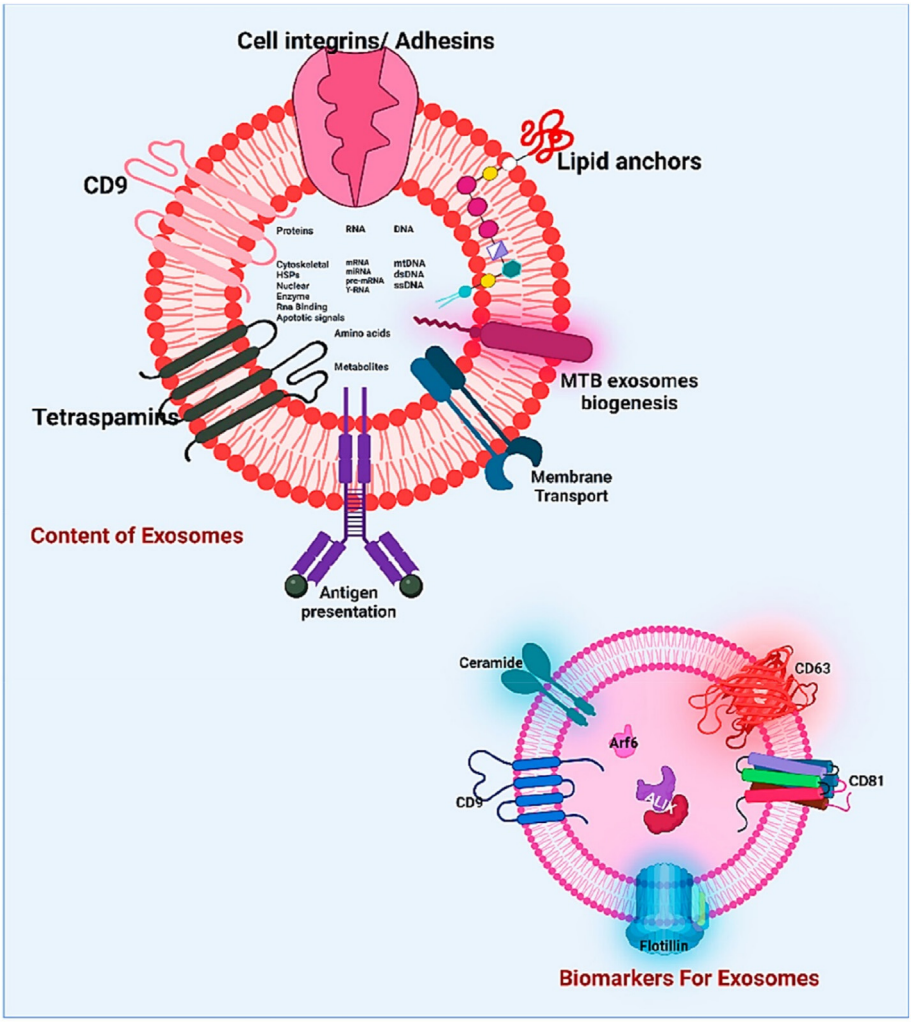

Fig. 1. The composition and structure of the exosome. DNA, RNA, Protein, and surface markers are among the several exosome-associated components essential in cancer biomarkers [42]. Copyright 2023 ACS Publications.

To treat gastrointestinal cancer, exosomes derived from bone marrow mesenchymal stem cells were modified with oxaliplatin and siRNA prodrugs. This approach led to precise tumor targeting and increased drug accumulation at the site, inhibiting adenocarcinoma growth in the pancreatic duct [69]. Additionally, exosomes have been utilized to treat liver and stomach cancer. These nanoparticles include miRNA inhibitors, which can selectively target cancer cells by controlling gene expression and arresting the development and metastasis of specific cells. The treatment of stomach and liver cancer has involved using modified exosomes containing miR-26a and macrophage-derived exosomes that carry exogenous miR-21 inhibitors [70,71].

Exosomes can have their cellular and tissue characteristics modified specifically to increase the efficacy and precision of medication administration. One example would be extracellular vesicles linked to the GE11 peptide and carrying oxaliplatin. This approach shows notable therapeutic success in treating colorectal cancer by focusing on cells expressing EGFR [72]. In a different instance, doxorubicin was delivered to colorectal cancer cells via exosomes that were altered with the AS1411 aptamer [73]. Functional exosomes, such as magnetic exosomes that are trackable by magnetic resonance imaging (MRI), can be used for targeted drug delivery. By applying an external magnetic field, these exosomes can accumulate at the tumor site and deliver the drug directly to the cancer cells [74,75]. Exosomes have a remarkable quality in that they may pass across the blood-brain barrier. Because of this characteristic, they may be created to transport therapeutic drugs such as curcumin and superparamagnetic iron oxide nanoparticles for the targeted therapy of gliomas. This approach makes them an excellent tool for treating brain malignancies [25].

3. Studies of exosomes as drug delivery system for cancer therapy

In an experimental investigation, Zhan et al. contrasted natural exosomes with amphiphilic phosphatidylcholine (PC) exosomes to determine which had more anticancer effects. According to their analysis, the introduction of PC into the blood reticulocyte-derived exosome's membrane lipid layer induces an approximately two-fold increase in the internalization of tumor cells by PC exosomes relative to regular exosomes. Additionally, PC exosomes loaded with therapeutic medicines demonstrated a significant increase in drug accumulation in tumor cells and demonstrated anticancer efficacy *in vitro* [77]. In clinical studies, Exosomes generated from dendritic cells have demonstrated a major function in triggering anticancer immune responses and causing cell death in tumor cells. A study that employed the surface modification method to deliver immune stimuli to dendritic cells (DCs) efficiently revealed that

Table 1
The relationship between exosomes and the promotion and development of various cancer types.

Origin of Exosome	Cancer Cell	Status	Application
CD44v6	Pancreatic and Colorectal cancer	*In Vivo/In Vitro*	CD44v6-competent tumor exosomes activate pancreatic and colon cancer cells by activating the Wnt/β-Catenin pathway [43].
Exosomal S100A9	Colorectal cancer	*In Vitro/In Vivo*	MDSC-derived exosomes (myeloid-derived suppressor cells) are intercellular messengers that increase the expression of S100A9 in granulocytic (G)-MDSCs [44].
Exosomal piRNA-17560	Breast cancer	*In Vitro/In Vivo*	Exosomal piRNA-17560 derived from exhausted neutrophils increases fat mass and obesity-related protein (FTO) expression in breast cancer cells [45].
Exosomal miR-301a	Pancreatic cancer	*In Vitro/In Vivo*	miR-301a-3p exosomes are produced by pancreatic cancer cells in a hypoxic microenvironment, and by activating polarized macrophages, they cause the development of malignant pancreatic cancer cells [9].
Exosomal miR-500a-5p	Breast cancer	*In Vitro/In Vivo*	Cancer-associated fibroblasts (CAFs) promote and signal cancer cell metastasis through exosomal miR-500a-5p [46].
miR-580-5p	Breast cancer	*In Vivo/In Vitro*	Exosomal miR-580-5p promotes breast cancer progression through CD44 expression [47].
miR-208a	Osteosarcoma	*In Vitro*	Exosomal miR-208a promotes osteosarcoma progression [48].
MiRNA-107	Gastric cancer	*In Vivo/In Vitro*	Exosomal miR-107 targets DICER1 and PTEN genes to induce their expansion and activity and thus may provide new conditions for gastric cancer progression [49].
MicroRNA-200b-3p	Lung cancer (Breast cancer lung metastasis)	*In Vivo/In Vitro*	Exosomal microRNA-200b-3p increases the expression of CCL2 in the lung, a prognostic factor for breast cancer lung metastasis [50].
MicroRNA-155-5p	Colon cancer	*In Vivo/In Vitro*	M2 macrophage-derived exosomal miR-155-5p leads to tumorigenesis by downregulating ZC3H12B gene expression and regulating inflammatory factor IL-6 expression [51].
GRP78-OE exosome	Gastric cancer	*In Vivo*	Exosomes containing GRP78 induce angiogenesis by strengthening the tumor microenvironment [52].
hsa-miR-24-3p	Liver cancer	*In Vivo/In Vitro*	hsa-miR-24-3p may become one of the most important molecular markers in liver cancer [53].
MicroRNA-497	Lung cancer	*In Vivo*	Exosomal miR-497 has inhibitory effects that can target tumor growth and angiogenesis and is targeted for cancer therapy development [54].
miR-186	Neuroblastoma	*In Vivo*	Nanoparticles containing exosomal miR-186 inhibit tumor growth in high-risk neuroblastoma patients by regulating TGFβ1 expression [55].
miR-21	Colon cancer	*In Vivo/In Vitro*	The delivery system of miR-21i exosome and 5-FU chemotherapy drug to HCT-1165FR cancer cells causes the downregulation of exosomal miR-21. It stops the cell cycle, reduces tumor proliferation, and increases apoptosis in colon cancer cells [56].
miR-381-3p	Breast cancer	*In Vitro*	Adipose-derived mesenchymal stem cells (ADMSC)-loaded exosomes with miR-381 inhibited the proliferation, migration, and invasive capacity of MDA-MB-231 cells and promoted their apoptosis *in vitro* [57].
Exosomal PD-L1	Systemic anti-tumor immunity and memory	*In Vivo/In Vitro*	Exosomal PD-L1 deletion inhibits tumor growth in models resistant to anti-PD-L1 antibodies. This mechanism can act as a therapy [58].
MicroRNA-30c	Ovarian endometriosis	*In Vivo/In Vitro*	Exosomal miR-30c reduces invasion and metastasis of ecto-EEC ectopic nodules by blocking the BCL9/Wnt/CD44 axis [59].
miR-30c-5p	Clear cell renal cell carcinoma	*In Vivo/In Vitro*	Urinary exosomal miR-30c-5p characterizes clear cell renal cell carcinoma at early stages by regulating HSPA5 gene expression [60].

exosomes derived from bovine serum modified with α-d-mannose caused them to bind to mannose receptors on the surface of DCs. This interaction activates the immune system, which can help combat infections and diseases, including cancer [78]. To activate the immune system against cancer, Zhu et al. demonstrated that modified tumor exosomes with a potent adjuvant termed HMGN1, a nucleosome-binding protein that attaches to the receptor on DC, boosted the protective immune response and activated T cells for around nine weeks [79].

Yang and colleagues assessed the cellular nanoporation technique's ability to produce exosomes with mRNA in large quantities to treat cancer. They started by transfecting plasmid DNA (PTEN and CDX) into cells from various sources. Next, they stimulated the release of exosomes containing mRNA by subjecting the cells to focal and brief electrical stimulation; these exosomes effectively inhibited tumor growth in glioma cells [80]. In different studies, Osman et al. looked at the efficacy of exosomes made from human red blood cells in treating leukemia. Exosomes target the human miR-125b-2 gene, an oncogenic miRNA linked to leukemia, and transport the Cas9 and gRNA. This study's findings demonstrated that these exosomes significantly reduce the expression of oncogene miRNAs. These results show immunological activation, drug accumulation, and targeted administration of therapeutic molecules, indicating the promise of exosomes as an efficient drug delivery vehicle for cancer treatment [81].

Exosomes were recovered by Qiao et al. from two cancer cell lines: Hela, which is human cervical cancer cells, and HT1080, which is human fibrosarcoma cells. The study demonstrated that HT1080 exosomes are considerably more absorbed by HT1080 cells than Hela exosomes. Consequently, it may be said that exosomes can return directly to the cancer cells from where they originated, meaning that they may deliver anticancer medications [82]. Kim et al.'s research has shown that exosomes may be utilized to introduce CRISPR/Cas9 to cancer cells and inhibit the formation of tumors. In this study, CRISPR/Cas9 was delivered by ovarian cancer exosomes (SKOV3-Exo). Their study aimed to inhibit the expression of the PARP-1 gene, which plays a role in the development and survival of tumors [83]. Exosomes containing berry anthocyanins were employed in a study to reduce the adverse effects of chemical drugs in ovarian cancer, and the study's outcomes were positive [84]. Wang et al. developed a novel approach to treating HER2+ breast cancer that would have fewer adverse effects. They delivered mRNA encoding the HChrR6 enzyme to HER2+ breast cancer cells via exosomes, which resulted in a nearly total growth halt of the cancer cells [85]. To treat estrogen receptor-positive (ER+) breast cancer, Caban et al. used exosomes produced from natural killer (NK) cells that were loaded with BCL-2siRNA. These exosomes efficiently enhanced apoptosis in breast cancer cells [86]. Research has shown that exosomes made from mesenchymal stem cells (MSC) are a potentially effective treatment for lung, ovarian, and breast cancer cells when used to deliver taxol to metastatic breast cancer tissue and other cancer cells [87]. Yu and colleagues created a novel strategy for breast cancer treatment in 2019. Their study showed that exosomes from human fetal lung fibroblasts may

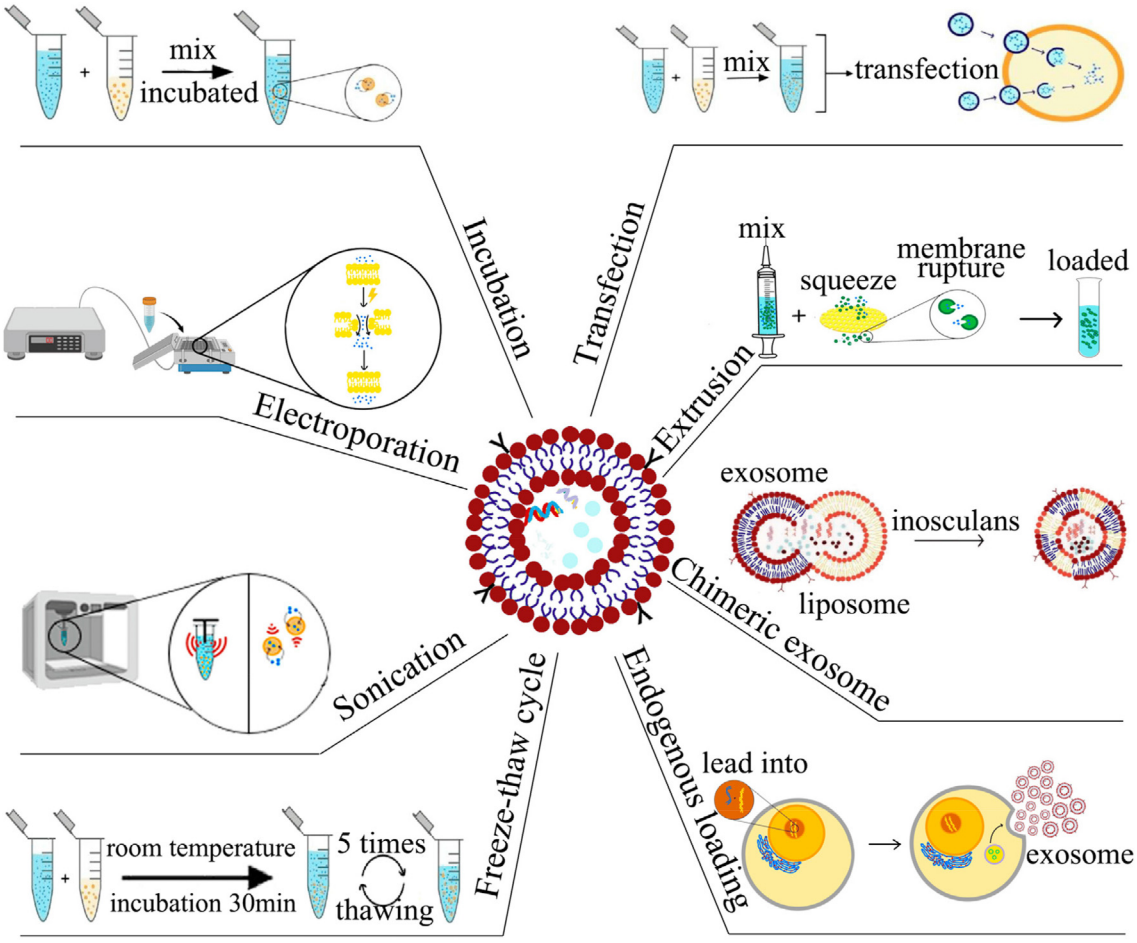

Fig. 2. Drug loading methods in exosome include freeze-thaw cycle (FTC), sonication, electroporation, incubation, extrusion, transfection, endogenous loading, and the chimeric exosome method. The effectiveness of exosomes' drug-loading depends on a variety of procedures carried out in a range of conditions [76]. Copyright 2023 MDPI.

dramatically reduce the migration and proliferation of MDA-MB-231 breast cancer cells when employed as a delivery system for the Errastin chemotherapeutic drug [88].

Exosomes derived from primary macrophages in the bone marrow were loaded with paclitaxel (PTX) by Kim et al. to treat lung metastases. These exosomes were then modified with aminoethylanisamide-polyethylene glycol (AA-PEG) to target the sigma receptor overexpressed in lung cancer cells. The results of the experiments demonstrated that engineered exosomes inhibited the growth of lung metastases in a targeted manner [89]. Exosomes were used in a study to deliver the drug celastrol to lung cancer cells, given that celastrol can stop the activation of the NF-κB pathway in cancer cells and induce cell death by creating stress in the endoplasmic reticulum of cancer cells. As a result, cholesterol-loaded exosomes can achieve significant antitumor effects [90]. Lin et al. designed a study to use iRGD-modified exosomes containing siCPT1A to overcome the drug resistance of colon cancer cells to oxaliplatin. Carnitine palmitoyl transferase (CPT)1A is a crucial enzyme in the fatty acid oxidation (FAO) pathway, and it is well-known that FAO contributes significantly to cancer cells' treatment resistance. Thus, by inhibiting CPT1A, exosomes containing siCPT1A decreased drug resistance in cancer cells in this research [91]. In a study by Li et al., doxorubicin (Dox) was delivered to colorectal cancer cells, specifically using antibody-modified A33-positive colon cancer cell-derived exosomes. Additionally, these exosomes were coupled to supermagnetic iron oxide nanoparticles, and these exosomes are particularly directed against A33-positive colon cancer cells [92].

A novel technique for removing pancreatic ductal adenocarcinoma (PDAC) was described by Zhou et al. They delivered gal-9siRNA and oxaliplatin (OXA), which kills tumor cells and causes apoptosis, using exosomes made from bone marrow mesenchymal stem cells (BM-MSCs). By stopping the product of galectin-9, siRNA protects the immune system against immunosuppression [93]. According to a study, transferring anti-c-Met siRNA via exosomes as a nanoparticle carrier offers a novel strategy for overcoming drug resistance and making gastric cancer cells more sensitive to cisplatin [24]. In a research, Exosomes were extracted from tumor cells and had been modified with the IL-2 gene to inhibit the growth of the tumor. The study's findings indicated that the exosomes could stimulate the proliferation and activity of T and NK cells and inhibit tumor growth [94].

4. Exosomal miRNAs and cancer

MicroRNAs (miRNAs) are small non-coding RNAs that control the expression of many genes and cellular pathways and play a major role in negative gene regulation [95,96]. Exosomal miRNAs are among the most important biomarkers in various biological processes, including regulating cell growth, differentiation, development, and apoptosis. Exosomal miRNAs are small particles that play important roles in cancer by controlling cell proliferation,

growth, and metastasis. New studies have shown that disturbances in the growth and proliferation potential of diseased or cancerous cells increase or decrease the expression of certain miRNAs in exosomes, which can lead to the development and progression of the disease. Therefore, an in-depth understanding of these miRNAs' role and function can help better understand the pathogenesis of diseases such as cancer and design more targeted treatments. Also, certain exosomes secreted by tumor cells can be used to predict the existence or presence of tumors in cancer patients [97–99]. The workflow of processing and using exosomal miRNAs for cancer clinical outcomes is depicted in Fig. 3 A.

A Study by Bhome and colleagues showed that exosomes from fibroblasts associated with colon cancer play an important role in cancer progression. These exosomes contain miRNAs that are delivered to cancer cells and affect cell proliferation and resistance to chemotherapy [100]. It has been reported in various studies that increased expression of miR-21 in fibroblasts enhances liver metastasis in animal models of colon cancer, indicating the importance of miR-21 in colon cancer progression [101,102]. Exosomal miRNAs of stomach and colon cancer play an important role in the diagnosis and prognosis of the disease. In gastric cancer, CD97 and exosomes promote the growth and invasion of cancer cells by activating the MAPK signaling pathway [103–105]. In colon cancer, exosomal miRNAs, including miR-17-3p and miR-21, are used as diagnostic and prognostic markers [106,107]. Therefore, studying exosomal miRNAs in body fluids can also be used as a new method to diagnose cancers, especially colon cancer [108–110]. Pancreatic cancer-derived exosomes also play an important role in the initiation of pre-metastatic origin in the liver. These exosomes contain factors such as macrophage migration inhibitory factor (MIF) that form pre-metastatic sites in the liver [111,112]. The level of exosomal miRNAs in the serum of patients with pancreatic cancer is increased compared to non-pancreatitis patients, especially miR 17-5p, which can be used as a marker for the spread and advanced stages of pancreatic cancer [113,114]. Studies have shown that the level of miR-21 in exosomes in the serum of patients with esophageal squamous cell carcinoma (ESCC) is increased compared to patients with benign tumors without systemic inflammation. Furthermore, exosomal miR-21 is associated with tumor progression and invasion. On the other hand, miR-34a is epigenetically reduced in ESCC [115–117]. It is mentioned in a study that cervical squamous cell carcinoma-excreted (CSCC) exosomal miR-221-3p transports into human lymphatic endothelial cells to promote lymph angiogenesis and lymphatic metastasis with down-regulation of vasohibin-1. This approach can indicate a new diagnostical biomarker and therapeutic target for metastatic CSCC patients in the early phases [118].

Fig. 3 B shows two examples of exosomal microRNAs that cause resistance to cisplatin through two different mechanisms. According to these mechanisms, exosomal miR-21 inhibits cell apoptosis by suppressing PTEN and stimulating the pro-tumorigenic PI3K/AKT pathway, which can increase resistance to cisplatin. Also, increasing exosomal miR-9 can suppress DNA damage repair in ovarian cancer and enhance ovarian cancer response to chemotherapy, such as cisplatin [98].

Exosomes have been considered new cancer markers because they can provide detailed information about tumor cells. Some of the advantages of these markers include high sensitivity, easy access to biological fluids, stability of miRNAs in exosomes, Low toxicity, compatibility with living tissues, prolonged blood circulation, ability to transport contents from one cell to another, non-immunogenic and specific targeting of different cells. However, there are problems such as the difficult isolation of exosomes derived from tumor cells, the varying quality and purity of isolation, and the need for precise normalization of miRNAs. In general, by conducting more research on exosomal miRNAs, we hope to provide new approaches for non-invasive cancer diagnosis [119–121].

5. Exosomes and cancer diagnosis

Due to the relative stability of vesicle compositions, which include a wide range of cancer-related biomarkers, exosomes are considered a powerful diagnostic tool [122]. The exosomes can transfer biomolecules from the main cancer site to nearby and distant cells to create a small environment for cancer growth and metastasis [123]. Also, due to their unique molecular and genetic content, which reflects the pathological state of the cells of origin, exosomes can be used as valuable biopsy samples to diagnose various diseases [124].

A study by Clark et al. showed that various proteins are collected in exosomes secreted by lung cancer cells, which can play a role in the occurrence of lung cancer and help in early diagnosis [125]. Exosomes can be used as effective carriers for the rapid diagnosis of diseases, the prediction of disease processes, and the response to

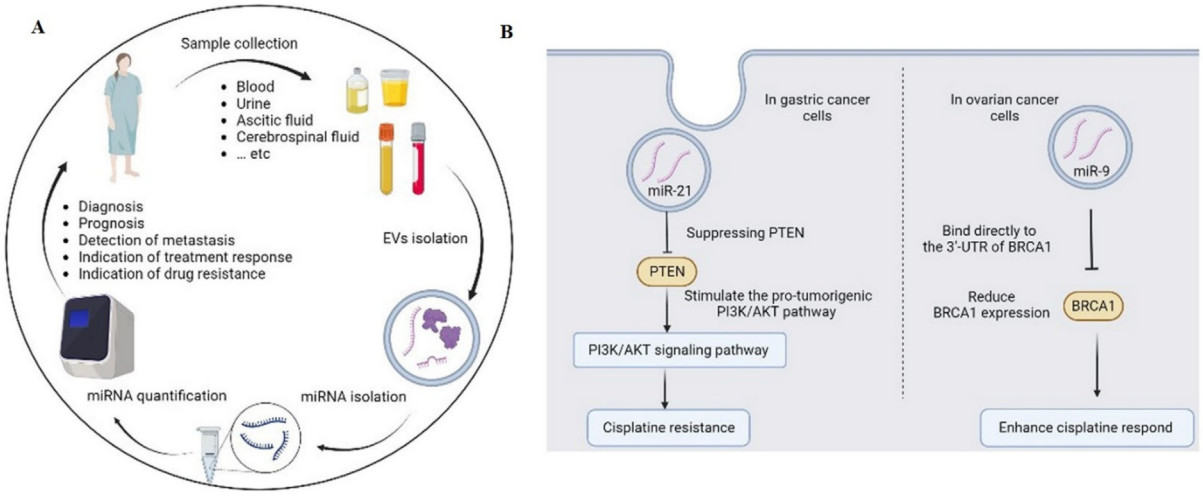

Fig. 3. Workflow for utilizing and analyzing exosomal miRNAs with clinical implications for cancer (A). Diagram showing two examples of exosomal miRNAs in cancer drug responsiveness and resistance [98]. Copyright 2023 Frontiers.

treatment of malignant tumors. Based on this research, exosomes containing proteins, nucleic acids and other molecules can provide important information. About the identity of the cancer and provide a set of signaling molecules that play a role in the processes of tumor progression and growth [126]. A study conducted by Fang et al. utilized a microfluidic chip for immunocapture and quantification of exosomes on 6 breast cancer patients and 3 healthy controls. It was shown that the expression levels of HER2 in exosomes were nearly consistent with those in tumor tissue assessed by immunohistochemical staining. This microfluidic chip may provide a new platform to aid in the diagnosis and molecular classification of breast cancer [127]. Domenyuk V et al., in a research, used an approach based on next-generation systems biology for exosome profiling of cancer patients' plasma. In this research, they showed that exosomes in plasma are very effective for identifying molecular patterns related to cancer [128]. It has been reported that the plasma exosomes of breast cancer patients contain Del-1 protein and the presence of this protein is very effective in the early detection of breast cancer [129]. Kibria et al. investigated a method for surface protein profiling of single circulating exosomes in human blood. Due to the sensitive and high throughput platform of single exosome analysis, this method can be used to analyze exosomes as diagnostic markers in cancer [130].

Exosome biomarker detection depends on the isolation technique and the most economical method, which provides the best area under the curve (AUC) and will probably be used in the clinic [131]. Fig. 4 shows an overview of the procedures used to identify extracellular vesicles (especially exosomes) as cancer biomarkers.

6. Exosomes and tumor microenvironment

Neoplasms include various subsets of tumor cells, cancer-related fibroblasts (CAFs), intrinsic and adaptive immune cells, secreted agents, and a wide range of extracellular matrix (ECM), which is collectively known as the tumor microenvironment (TME) [132]. Low oxygen rates, high lactate rates, extracellular acidosis, and little nutritional amount are eminent characteristics of TME [133]. Many cancer cells release Extracellular vesicles (EVs), consequently affecting TME and suppressing or stimulating immune responses, leading to a delicate balance of immune modulation [134]. Under physiological conditions, exosomes can have various biological and cellular functions. However, a change in their function may lead to cancer [135]. Exosomes have appeared as critical factors in extracellular communication [136]. The most important role of exosomes is to establish cell-cell communication across body distances, including the microenvironment of cells [137,138].

A study showed that colorectal cancer cells deriving exosomal miR-934 induce M2 macrophage polarization by downregulating PTEN expression and activating the PI3K/AKT signaling pathway, promoting liver metastasis. Consequently, exosome-mediated interactions among cancer cells and surrounding cells renovate the TME, establishing a favorable condition for cancer development and metastasis [139]. It is reported that tumor cells have changed inflammatory and hypoxia-associated signaling and secrete exosomes at rates higher than non-tumor cells [140]. For example, it was determined that a mechanism through which hypoxia in glioma impacts autophagy and M2-like macrophage polarization via exosomes could progress the development of the immunosuppressive microenvironment. In addition, IL-6 and miR-155-3p are increasingly expressed in hypoxic glioma-derived exosomes and are transferred to macrophages via exosomes [141].

Hypoxia-inducible factor 1 (HIF-1) is a key regulator of metabolic reprogramming in hypoxic cancer cells [142]. Cancer cells express HIF-1 at a high level when hypoxic conditions are created, and HIF1 regulates the metabolism of cancer cells in these conditions [143]. It is reported that the hypoxic-expression exosomal circZNF91 transmitted into normoxic pancreatic tumor cells and could competitively attach to miR-23b-3p, which prevents the suppression of miR-23b-3p on the expression of the deacetylase Sirtuin1. Therefore, the

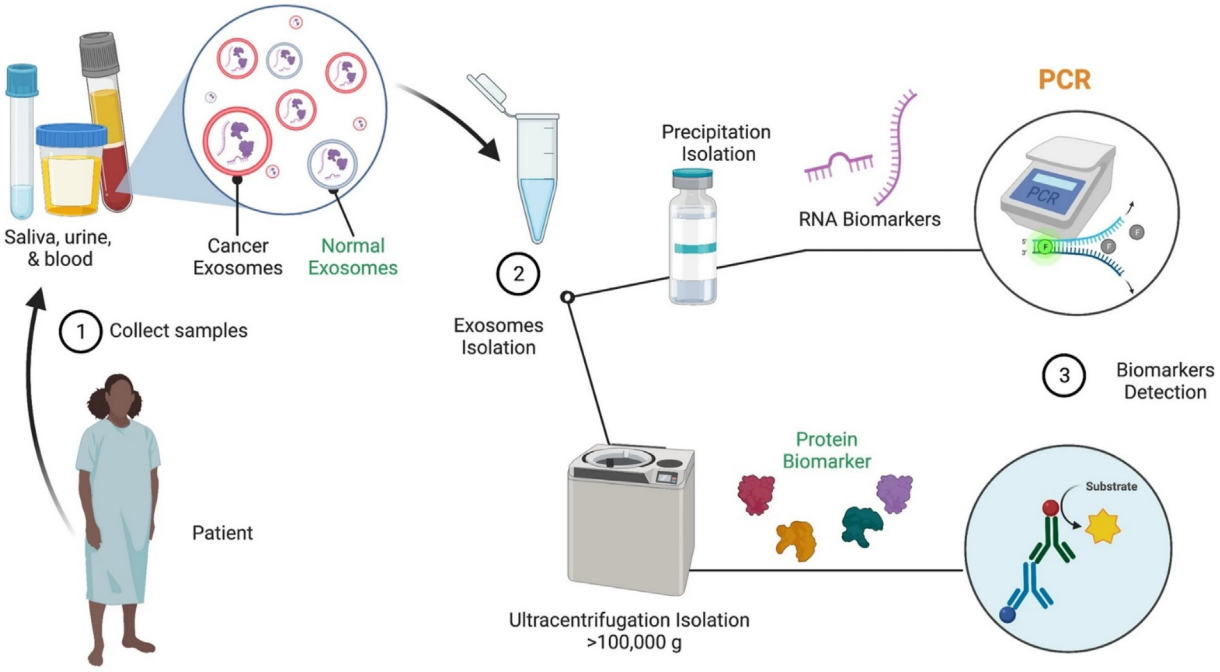

Fig. 4. Techniques applied to isolate tumor-derived exosomes and detect their biomarkers in personalized medicine. Step 1: Obtain a sample of the patient's biofluid, such as blood, urine, or saliva. Step 2: Using a range of techniques, separate the exosomes from these samples. Step 3: Using a variety of techniques to identify tumor-derived exosomes, including PCR or RNA sequencing for RNA; and ELISAs, western blots, or mass spectrometry for proteins; and multiplexed microarrays. These techniques are all dependent on isolation. The pairing of methods can be critical to optimizing biomarker discovery [131]. Copyright 2024 BMC.

upregulated Sirtuin1 increased the deacetylation-dependent sustainability of the HIF-1α protein, leading to glycolysis and Gemcitabine chemoresistance of recipient pancreatic cells [144].

7. Exosomes and cancer drug resistance

Drug resistance is one of the most important challenges in cancer treatment. Understanding this mechanism is very important for effective treatment. There are two forms of drug resistance in cancer: internal resistance that is created before treatment, along with restrictions on the use of anticancer drugs, and acquired resistance that is created during treatment. Drug resistance effectively affects chemotherapy, thus leading to adverse effects and tumor recurrence [145,146]. Unfortunately, drug resistance has seriously affected patient survival worldwide. As intercellular messengers of the TME, exosomes have been proposed as a new approach to establish and transfer therapeutic resistance in cancer and help in cancer treatment, which can promote the angiogenic phenotype and cell-to-cell adhesion in target cells [147,148]. Three exosome-mediated drug resistance mechanisms have been defined: drug delivery through the exosome pathway, antibody-based drug neutralization, and miRNA-mediated exosome delivery [149].

Exosomal miRNAs contribute to drug resistance in cancer cells by disrupting drug transport and metabolism. They modulate the activity of the human ATP-binding cassette (ABC) transporter superfamily, leading to drug efflux mechanisms. In drug-resistant cancer cells, upregulated ABC transporters pump out anticancer drugs, reducing their levels. Exosomal miRNAs derived from tumors, such as miR-1246 released by ovarian cancer cells, can suppress Cav1 expression and regulate ABCB1 expression, promoting a tumor-supporting phenotype and drug resistance [150]. In pancreatic adenocarcinoma, tumor-associated macrophages release exosomes containing miR-365, contributing to resistance against gemcitabine [151]. Drug-resistant cancer cells can encapsulate chemotherapeutic agents in exosomes and use these vesicles to transport anticancer drugs out of the tumor cell, reducing their effectiveness [152]. A study has shown the remarkable role of exosomic miR-155 and miR-21 in the cross-talk between human monocytes and neuroblastoma cells in the resistance to chemotherapy via a novel exosomic miR-21/TLR8-NF-κB/exosomic miR-155/TERF1 signaling pathway [153].

It has been reported that exosomes released by tamoxifen-resistant MCF-7 cells had higher expression of miR-222, whereas miR-222 down-expression makes MCF-7 more susceptible to tamoxifen. Moreover, P27 and Estrogen receptor alpha (ERα) expression increased at both the mRNA and protein levels compared to tamoxifen-resistant cells [154]. Consequently, exosomal miR-222 might regulate P27 and ERα in ER-positive breast cancer cells, which could mediate tamoxifen resistance. Cancer-secreted exosomes, except for miRNAs, also function as mediators of drug resistance by transporting certain proteins that could be regulated by an associated network. The human MDR1 gene on chromosome 7p2 produces P-glycoprotein (P-gp), a component of the ATP-binding cassette, also known as the drug transporter [155]. MCF-7/DOC/exos express P-gp more than MCF-7/exos [156], and MCF-7 cells incubated with MCF-7/DOC/exo exhibit a decreased rate of cell apoptosis in contrast to MCF-7 cells. Consequently, it suggests that P-gp from MCF-7/DOC cells may be transferred by exosomes to sensitive cells, thereby reducing the chemosensitivity of breast cancer cells [157]. It has been reported that Docetaxel resistance is related to the enhancement of exosome secretion in a prostate cancer model, probably due to docetaxel efflux through exosomes. However, this hypothesis has not been proven in any breast cancer model and should be verified through further studies [158,159].

Exosomes influence the activity of immune cells and can change survival pathways and the expression of drug-resistant genes. This approach can impact tumor cells' susceptibility to chemotherapy and accelerate the formation of drug resistance [160,161]. It is essential to understand the various ways that exosomes cause tumor drug resistance, such as resistance to drugs in ovarian cancer, is critical for developing novel therapeutic approaches to overcome these challenges (Fig. 5).

8. Exosomes and tissue renewal/regeneration

Exosomes derived from stem cells, particularly those from mesenchymal stem cells (MSCs), have demonstrated the ability to promote tissue regeneration in a range of conditions. These include neurological disorders, autoimmune diseases, inflammatory diseases, cancer, heart disease caused by ischemia, lung injuries, and liver fibrosis [163]. The precise function of exosomes derived from mesenchymal stem cells (MSCs) in cancer treatment, particularly regarding tissue repair, remains largely unclear [164]. The potential role of exosomes derived from stem cells in tissue repair related to cancer can be analyzed from multiple perspectives: one aspect involves exosomes associated with cancer stem cells (CSCs), while the other pertains to exosomes that contribute to wound healing in conditions like gastric ulcers and liver fibrosis, which have a higher risk of progressing into cancer [165–169]. Exosomes produced by CSCs can maintain a stable environment within tumors, promoting self-renewal. They also influence nearby or distant cells to aid cancer cells in evading the immune system and inducing immune tolerance [170]. This approach could lead to the creation of innovative clinical diagnostic and prognostic tools, as well as therapies that help prevent tumor resistance and recurrence. Exosomes derived from CSCs contain factors like OCT-4, SOX-2, and NANOG, as well as lncRNA/microRNA. These components interact with nearby cells to increase the expression of stemness traits, contributing to cancer progression [168,171].

Additionally, exosomes derived from CSCs stimulate neoangiogenesis and facilitate metastasis. Healthy endothelial cells can trigger pathways that promote the growth of new blood vessels by absorbing exosomes released by cancer cells. Research has demonstrated that exosomes derived from CSCs can convert healthy fibroblasts into cancer-associated fibroblasts (CAFs) with heightened oncogenic capabilities. This transformation occurs by up-regulating the β-catenin/mTOR/STAT3 signaling pathway and elevating both mRNA and protein expression of TGF-β1 [172]. Another research revealed that the long non-coding RNA DOCK9-AS2, carried in exosomes from cancer stem cells of papillary thyroid carcinoma (PTC), can stimulate the Wnt/β-catenin signaling pathway. This activation enhances stemness and promotes proliferation, migration, and invasion capabilities in PTC [173]. Exosomes produced by CSC enable cancer cells to escape the immune system. The results of a study demonstrated that exosomes expressing PD-L1 can suppress the antitumor responses of T cells. In melanoma patients, exosomal PD-L1 serves as an indicator of immune activation shortly after starting treatment with PD-1-blocking antibodies and can predict the clinical effectiveness of PD-1 blockade therapy [174]. CSCs use exosomes to secrete factors like IL-6, IL-8, IL-1β, and VEGF, which recruit and activate stromal cells, reorganize the ECM, and promote metastasis, drug resistance, and tumor progression [175,176].

In contrast to healthy tissues, exosomes derived from CSCs promote undesirable self-renewal and regeneration of cancer cells (Fig. 6 A). Instead of restoring healthy tissue function, these processes drive tumor growth, metastasis, and resistance to treatment

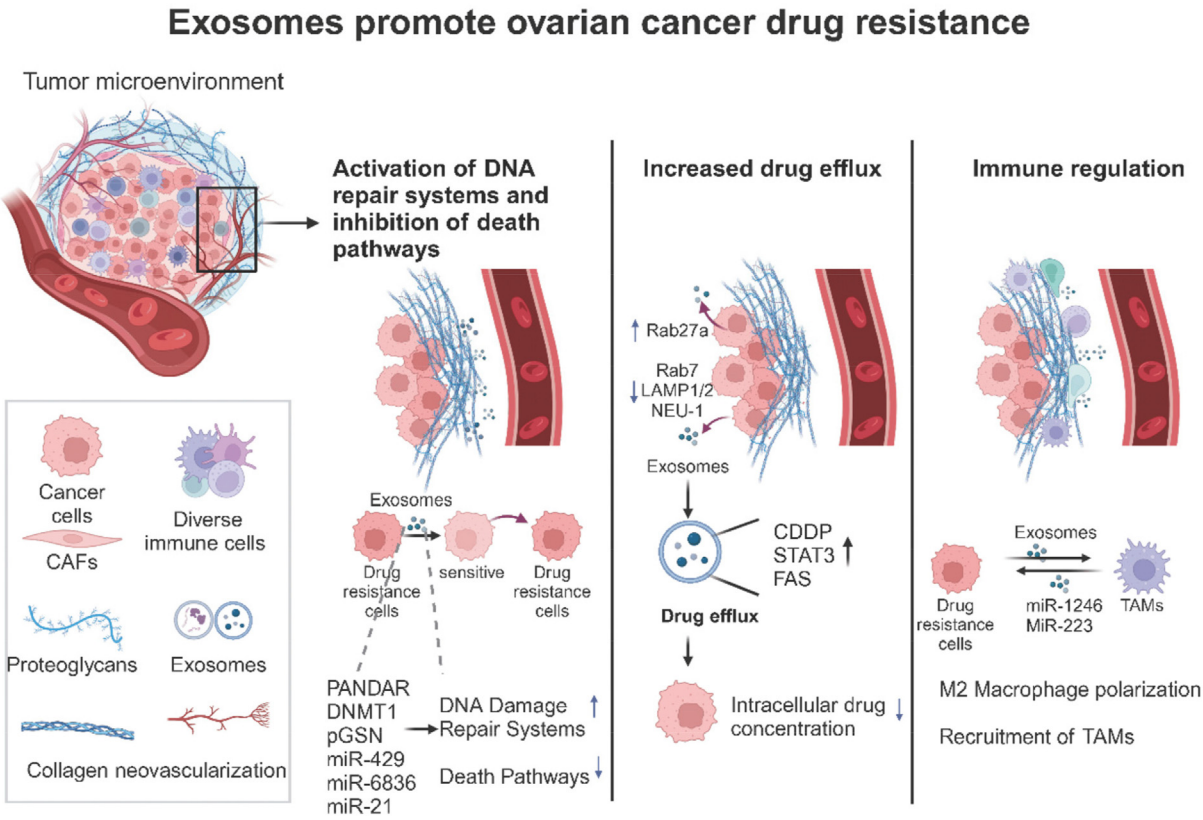

Fig. 5. The function of exosomes in ovarian tumor drug resistance. Exosomes in the ovarian cancer tumor microenvironment promote drug resistance through three main pathways: 1. Activating DNA repair and inhibiting death pathways in tumor cells 2. Promoting drug efflux to reduce intracellular drug concentrations in tumor cells 3. Modulating immune cells to create an immunosuppressive microenvironment [162]. Copyright 2024 MDPI.

targeting and suppressing exosomes produced by CSCs may offer a strategy to block tumor development and potentially enhance the effectiveness of chemotherapy. Numerous studies have demonstrated that eliminating HRS, STAM1, and TSG101 decreases the release of exosomes, and disrupting these ESCRT (endosomal sorting complexes required for transport) components alters the characteristics and contents of the vesicles. In addition to the ESCRT-dependent sinaling pathway, exosome production is also influenced by the sphingolipid ceramide. This process can be inhibited by GW4869, which blocks acid sphingomyelinase activity. Furthermore, the Rab27 family, a set of small GTPase proteins, is crucial for the secretion of exosomes. Inhibiting Rab27a expression using RNA interference decreases exosome release in cancer cells, consequently restricting tumor progression and the formation of metastatic clones [177,178]. CSC-derived exosomes, reflecting cellular content and carrying specific markers, could be targeted to interfere with their synthesis or effects. Their unique miRNA and protein profiles in cancer patients' fluids differ from normal ones, offering potential as early diagnostic and prognostic tools for metastasis. CSC exosomes play a critical role in cancer progression and may help identify primary tumor niches and pre-metastatic niches for early intervention [179,180]. Targeting exosome molecules like miR-21 and lncRNA UCA1 shows promise for treating aggressive cancers [181]. Researchers have used exosome-like nanoparticles to target liver CSCs, reprogram CSCs, and stimulate differentiation [182]. Other research using *in vivo* models has also explored the potential clinical applications of targeted exosomes., for example, biocompatible exosome-biomimetic nanoparticles (PSiNPs) for targeted chemotherapy, showing strong cellular uptake and cytotoxicity in cancer cells and CSCs [182,183].

Regeneration and repair of some tissues, such as the liver, as well as stomach ulcers and colorectal disease, is vital because lack of proper treatment may lead to progression to disease and cancer [184,185]. Research has demonstrated that exosomes released by BMSCs can enhance hepatocyte regeneration, suppress α-smooth muscle actin (α-SMA) expression, and primarily inhibit the activation of hepatic stellate cells (HSCs) via the Wnt/β-catenin signaling pathway, thereby reducing liver fibrosis [186]. MiR-199a-3p influences the proliferation, migration, and invasiveness of hepatocellular carcinoma (HCC) cell lines, enhancing their sensitivity to adriamycin. Lou et al. created exosomes (AMSC-Exo-199a) via miR-199a lentivirus infection, resulting in over tenfold higher miR-199a-3p levels compared to controls. Additionally, the overexpression of miR-199a-3p in these exosomes inhibited the mTOR signaling pathway, further increasing HCC sensitivity to chemotherapy [187]. Zhang et al. conducted a study using TNF-α pretreated umbilical cord mesenchymal stem cell-derived exosomes (T-Exos) to treat an acute liver failure (ALF) mouse model. They observed an increase in miR-2993p levels in T-Exos, which has anti-inflammatory properties and inhibits the NLRP3 inflammatory pathway. This led to reduced serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and pro-inflammatory cytokines, resulting in less inflammatory damage and enhanced liver tissue repair [188]. Another research found that MSC-derived exosomes (MSC-EXOs) can prevent liver fibrosis by transporting miR-148a. This microRNA influences the function of macrophages within the liver through the KLF6/STAT3 signaling pathway, offering a potential treatment option for liver fibrosis [189]. Acute-on-chronic liver failure and cirrhosis, the end stage of chronic liver disease, are major risk factors for hepatocellular carcinoma and limit anticancer therapy

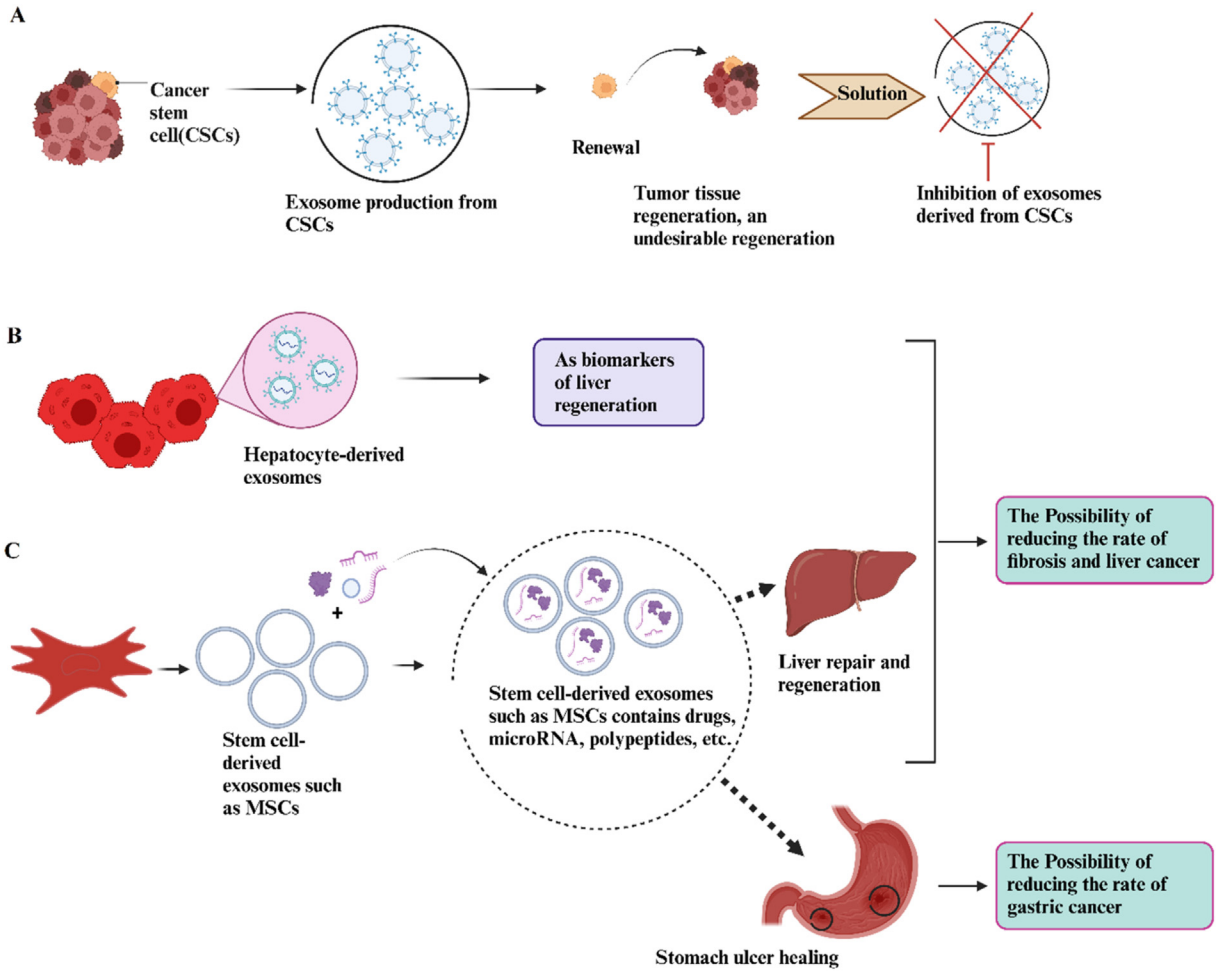

Fig. 6. Exosomes produced by CSCs can maintain a stable environment within tumors and promote self-renewal, leading to an undesirable repair and regeneration of tumor tissues (A). Hepatocyte (B)- and MSCs-derived exosomes (C) are crucial for the regeneration and repair of some tissues, such as the liver, as well as gastric ulcers, as lack of proper treatment may lead to disease progression and cancer. Created with BioRender.com.

for liver and other malignancies [190–192]. Exosomes have the advantage of specificity in noninvasiveness in peripheral blood and liver biopsy, and they may be a potential biomarker of liver disease. Accordingly, a study by Jiao et al. showed that hepatocyte-derived exosomes may serve as biomarkers of liver regeneration and prognostic value in patients with acute-on-chronic liver failure (Fig. 6 B) [193]. Their study found that the exosome profiles containing Albumin and VEGF may serve as more precise biomarkers for liver regeneration and prognosis compared to alpha-fetoprotein in patients with acute-on-chronic liver failure. Additionally, exosome profiles with CD63 and Albumin could act as early-warning indicators for these patients [193]. Research has indicated that exosomes produced by mesenchymal stem cells can lower serum aminotransferase levels, reduce tissue necrosis, boost the population of Ki-67-positive hepatocytes, and suppress the transcription of genes associated with inflammation. These effects suggest that these exosomes have the potential for regenerative effects (Fig. 6 C) [194,195].

The successful application of transplanted mesenchymal stem cells in healing gastric ulcers has sparked interest in exploring their impact on the neovascularization of tumors and potential anti-angiogenic treatments. These treatments could utilize secretions from MSCs, such as exosomes, to target gastric cancer cells (Fig. 6 C) [169]. Colorectal cancer (CRC) occurs more commonly in individuals with long-standing ulcerative colitis (UC) and is among the most severe and potentially fatal complications associated with UC [196]. Human umbilical cord mesenchymal stem cells (hUC-MSCs) are vital in regenerating tissues after injury and inflammation. Growing preclinical studies indicate that exosomes obtained from hUC-MSCs (hUCMSC-Exo) can amplify the therapeutic impacts of these stem cells and offer protective effects against tissue injury in UC [197–200]. Exosomes from human umbilical cord-derived MSCs, bone marrow-derived MSCs, adipose-derived MSCs, and olfactory ecto-MSCs have been shown to enhance recovery in experimental UC by inhibiting inflammatory cells such as macrophages and Th1/Th17 cells, reducing pro-inflammatory cytokines, and boosting the anti-inflammatory effects of Treg and Th2 cells. Furthermore, exosomes from human bone marrow and umbilical cord MSCs that contain tumor-suppressive microRNAs (miR-3940-5p, miR-22-3p, miR-16-5p) can impede the proliferation, migration, and invasion of CRC cells by modulating the RAP2B/PI3K/AKT signaling pathway and ITGA2/ITGA6 [201,202].

9. Conclusion and prospects

The vesicles known as exosomes are nanoscale particles that facilitate communication both intra-cellular and inter-cellular. Exosomes are increasingly being shown to be crucial to developing pathogenic diseases. Exosomes may serve as biomarkers for different types of cancer. Exosomes can transport drugs that target

a variety of cancer cells. In this article, we reviewed studies on the role of exosomes in different fields of cancer, including drug delivery, tumor microenvironments, drug resistance, exosomal microRNAs, and cancer diagnosis. Clinical trials on exosomes are just beginning, revealing their crucial role in cancer progression and prognosis prediction. However, many properties and mechanisms of exosomes remain unclear, with conflicting results from various studies likely due to variations in culture conditions and purification methods. Standardized, cost-effective protocols for exosome production are essential for research. Furthermore, even though exosomal proteins and miRNAs have potential as cancer biomarkers, further research is needed to determine how well they work for diagnosis and treatment [203].

CSCs release exosomes that repopulate tumors and promote unwanted repair and regeneration, and these types of exosomes should be inhibited. Meanwhile, exosomes derived from other cells, such as hepatocytes and mesenchymal stem cells, are critical for healing organs such as the liver and healing stomach ulcers. Without proper treatment, this healing process can backfire, potentially leading to disease progression or even cancer. Identifying these exosomes seems essential for healing other tissues, including lung tissue, and preventing the spread of disease and cancer. Understanding the specific molecular profiles of tumor-derived exosomes is vital for predicting prognosis and assessing metastasis risk. Overall, clarifying the role of exosomes in cancer could significantly impact treatment approaches, paving the way for personalized medicine. More studies, including preclinical and clinical research, are needed to understand the role of exosomes in cancers better.

Authors' contributions

MS and ZA participated in designing, writing, revising, and preparing the manuscript Figures. All authors contributed to writing the manuscript and also read and approved the final version.

Ethical approval

This review paper contains no studies on animals or human participants performed by authors.

Funding

This review article was supported by a small grant from Fasa University of Medical Sciences, Fasa, Iran [Project Code: 403073].

Declaration of competing interest

The authors declare that they have no conflict of interest.

Acknowledgments

The authors want to acknowledge that Fasa University of Medical Sciences provides research facilities.

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