

REVIEW

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Emerging applications of extracellular vesicles in tumor therapy

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Abstract

Extracellular vesicles (EVs) have tremendous potential as nano/micron-sized drug delivery carriers. Their physical, chemical and biological characteristics distinguish them as unique carriers with specific pharmacokinetic, circulating metabolic, and biodistribution patterns in the delivery of therapeutic cargoes. They are critical mediators in the pathology of many diseases, including inflammatory diseases, fibrosis, and cancer, but they are also essential mediators in immunomodulation, cancer treatment, infectious defense, and tissue repair. In this review, we emphasize recent advances in oncology therapy using macrophage EVs, mesenchymal stem cell EVs, milk EVs, and plant EVs, as well as the advantages of EVs as delivery platforms and their prospective clinical applications and use.

Keywords: Extracellular vesicles, Exosomes, Nanotechnology, Drug delivery, Tumor therapy

Introduction

Cancer is one of the most important burdens that humanity faces today. According to the World Health Organization, cancer is responsible for one out of every six fatalities worldwide. Despite increasing anticancer treatment efficacy, cancer mortality rates continue to increase worldwide (Maeda and Khatami 2018). Cancer's persistence is a significant impediment to its cure, and factors such as tumor recurrence, inappropriate physicochemical properties of anticancer drugs, and the related poor pharmacokinetic profile frequently affect treatment efficacy (Minchinton and Tannock 2006). Among these disadvantages, multidrug resistance (MDR) is one of the primary causes of poor efficacy, which is accomplished by decreasing cancer's responsiveness to common chemotherapeutic agents. Overexpression of efflux pumps (Giddings et al. 2021), hypoxic condition of the tumor microenvironment (TME) (Robey et al. 2005), epigenetic modifications (Assaraf et al. 2019) and the influence of cancer stem cells (Zhou et al. 2021) are the factors involved. Therefore, new therapeutic modalities are required to enhance the treatment of tumors, and EVs—an emerging nanomaterial—has a promising future as diagnostic and therapeutic carriers (Wang et al. 2021a; Zaimy et al. 2017; Dadwal et al. 2018; Jeswani et al. 2018; Feng et al. 2022).



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EVs are small lipid membrane vesicles that are secreted into the extracellular space by almost all cell types. EVs play an essential role in information transport, transporting cargoes of packaged cellular proteins, nucleic acids, and metabolites from the parent cell to the recipient cell and mediating significant intercellular communication in physiological and pathological processes (Cianciaruso et al. 2019; Wang et al. 2020; Pu et al. 2021; Barone et al. 2022). Several isoforms of EVs regulate autocrine, paracrine, and endocrine functions (Record et al. 2014; Ela et al. 2013; Xu et al. 2013). EVs play a significant role in the progression of tumors. Both tumors and non-tumors secrete EVs, which can spread and impact different cell types at the initial tumor site as well as in distant organs. These EVs, which are frequently identified in the tissues and bodily fluids of cancer patients, are important mediators that mediate cellular communication between tumor cells and stromal cells in the local and distant metastatic microenvironment, coordinating multiple systemic pathophysiological processes (Becker et al. 2016). Thus, EVs can be used not only as diagnostic markers for tumors but also as anti-cancer therapeutic agents and anti-cancer vaccine delivery vehicles. As the function of EVs has been studied, there is increasing evidence that EVs can play an important part in disease progression (Feng et al. 2022; Wang et al. 2020, 2021b). Therefore, a comprehensive understanding of EVs and their role in disease pathology and treatment will provide us with novel approaches to the treatment of tumors in the coming clinical settings.

Extracellular vesicles

Pan and Johnstone described EVs as a heterogeneous collection of membrane structures containing intracellular molecules that are widely present in biological fluids (Street et al. 2012; Reinhardt et al. 2012; Taylor and Gerçel-Taylor 2005; Runz et al. 2007; Fernández-Llama et al. 2010; Chen et al. 2010; Admyre et al. 2007; Levänen et al. 2013; Pan and Johnstone 1983). Earlier research indicated that EV release was part of a processing mechanism for removing unwanted material from the cell. As research advanced, it was discovered that the release of EVs was also an important mediator of intercellular communication, involved in both normal physiological and pathological processes. EVs are classified into two types based on their size: 50–1000 nm vesicles produced by plasma membrane germination, which include exfoliated vesicles, microparticles and microvesicles (MVs), and apoptotic vesicles; and 40–160 nm sized exosomes from somatic cells (Kubo 2018).

In the cytoplasm, EVs are produced and degraded. Early endosomes are created via lipid raft-mediated endocytosis, while endosomes are formed through invagination of the plasma membrane. Early endosomes split into circulating endosomes after a portion of them fuses with endocytic vesicles (Morelli et al. 2004). The remaining early endosomes germinate inward and absorb nucleic acids, proteins and other substances to form intraluminal vesicles (ILVs), which gradually develop into late endosomes—the so-called multivesicular bodies (MVBs) (Stoorvogel et al. 1991). These MVBs can combine with lysosomes for degradation or with cell membranes to release exosomes into the extracellular environment (Grant and Donaldson 2009). Recent evidence suggests that Rab5–Rab7 GTPases are converted by SAND family proteins during the maturation of endosomes (Rink et al. 2005). The critical switch for Rab conversion is SAND-1/Mon1, which displaces RABX5 from the endosomal membrane, interrupts the positive

feedback loop of RAB5 activation, and extends its recruitment by interacting with the HOPS complex, allowing RAB7 to be recruited at the same membrane (Poteryaev et al. 2010; Singh et al. 2014) (Fig. 1).

Advantages of EVs as a drug delivery system (DDS)

Size (Lerch et al. 2013), shape (Mitchell et al. 2021) and surface charge (Jeon et al. 2018) are presently known to influence the internalization of nanomaterials by cells. Furthermore, the stiffness of nano/micro materials, whether natural or engineered, is an essential factor in cellular phagocytosis (Dai et al. 2019). Exosomes have many unique characteristics, including good biocompatibility, low immunogenicity, minimized size, abundant surface proteins, and equipped molecular content, indicating their potential as excellent drug delivery carriers. EVs have a superior shuttling ability to cross biological barriers, and their specific homing affinity for their initial organ of origin helps to avoid liver traps (Qiao et al. 2020), and they can also effectively cross the blood–brain barrier (BBB) (Betzer et al. 2017; Shahjin et al. 2020) and the autophagy-lysosome pathway (Skotland et al. 2017; Polanco et al. 2021). Furthermore, EVs may remain in tumors for longer than other nanoparticles (Abello et al. 2019), have lower clearance rates (Belhadj et al. 2020), are more precisely localized, are more widely available, can be completely degraded and recovered in vivo, and have significant therapeutic effects as natural biologics rather than synthetic materials (Fu et al. 2021).

Our frequently used pharmaceutically active biomolecules include chemotherapeutic drugs, hormones, peptides, cytokines, proteins, and therapeutic oligonucleotides, and their physicochemical properties and route of administration have a significant impact on their biosafety and efficacy. EVs have a better safety profile, higher capacity, and the presence of small functional peptides on their surface for improved targeting as a medicinal carrier when compared to other carriers (Zhang et al. 2020). Furthermore, in clinical

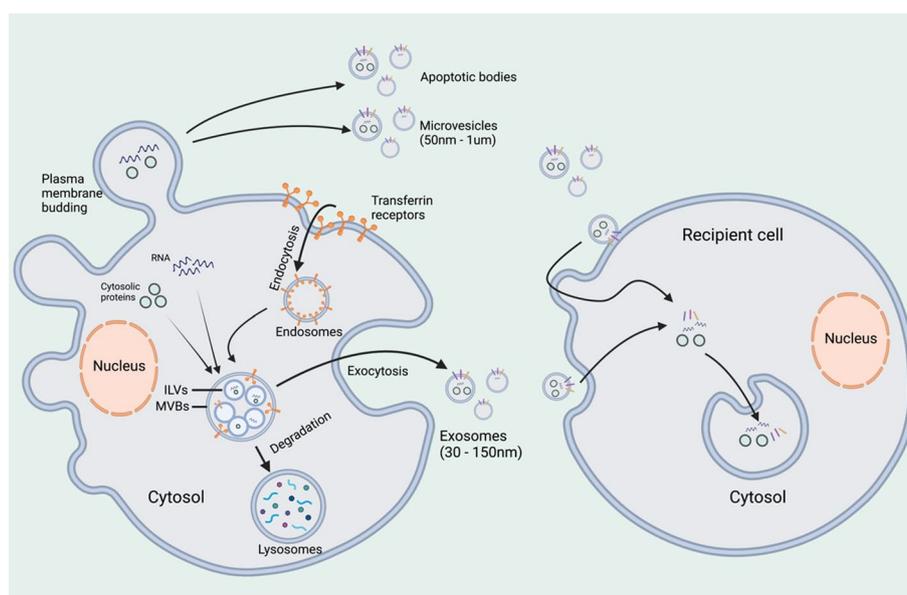


Fig. 1 The process of extracellular vesicle generation, secretion and uptake by receptor cells

applications without delivery assistance, many conventional anticancer drugs, such as paclitaxel, doxorubicin, and curcumin, show low water solubility, short half-life, and poor stability, necessitating frequent high-dose administration. Loading the drug into EVs improves drug stability and bioavailability, maximizes retention in the target lesion, and greatly improves efficacy when compared to free delivery (Walker et al. 2019; Lin et al. 2019). Figure 2 shows the current common process of EVs as drug carriers against tumors.

In conclusion, as emerging nanotechnologies, the clinical application of EVs could provide a versatile delivery platform for next-generation therapies and usher in a new age of cell-free therapy. Needless to say, tailoring preventive or therapeutic interventions to those who will profit the most adds significant value to the development and practice of precision medicine.

Emerging EVs technology in tumor treatment

Role of EVs in tumor microenvironment (TME)

TME plays a crucial part in the development and prognosis of tumors. Extracellular matrix (ECM), stromal cells, various infiltrating immune cells, and cancer cells all work together to generate a dynamic, heterogeneous environment known as a solid tumor (Galli et al. 2020). Because of interactions between various components that resulted in ongoing epigenetic and functional plasticity, tumor and stromal cells have co-evolved. There are several methods to treat tumors by remodeling TME, and therapeutic approaches that target TME are a reliable strategy. This treatment can cross the physical barrier, but it is challenging to avoid causing excessive alterations to its supramolecular structure, which may lead to the spread of metastases in vivo (Chen et al. 2022a; Chiang and Lo 2014).

Due to the characteristics of EVs, this makes it crucial in TME. Tumor-derived EVs affect immune system homeostasis primarily by inducing immunosuppressive changes that shield the tumor. They can also stimulate epithelial cells to release factors involved in EMT, which results in the spread of tumor cells. Extracellular matrix remodeling and tumor invasion can also be caused by tumor-derived EVs (Becker et al. 2016).

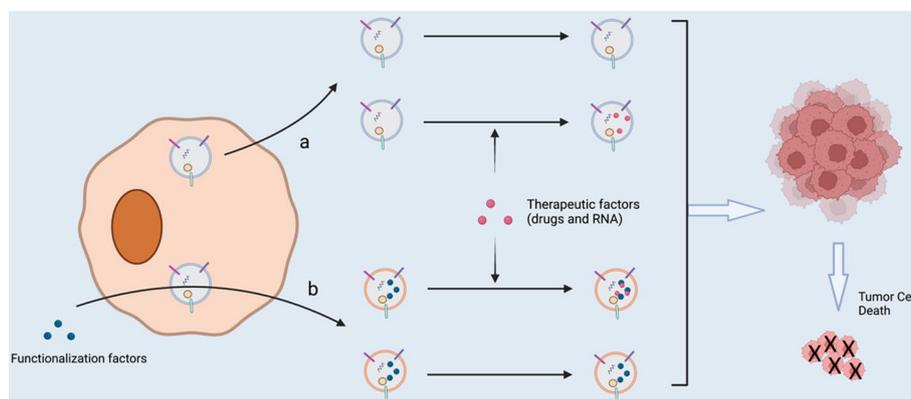


Fig. 2 **a** Functional cells release EVs to act directly or act on tumor cells after loading therapeutic factors. **b** EVs released by functional cells after modification of some functional factors act directly or act on tumor cells after loading therapeutic factors

Therapeutic EVs that target TME have emerged in this context. When applied to tumor cells or solid tumors, EVs that can modify TME or EVs containing drugs have been found to have positive therapeutic effects. The impact of tumor-derived EVs and therapeutic EVs on the TME is depicted in Fig. 3.

Macrophage-derived EVs

Macrophages (M ϕ) are highly heterogeneous immune cells that are widely involved in the pathological processes of various diseases and are closely linked to the tumor micro-environment and cancer cell metabolism. Macrophages are classified into two kinds based on their microenvironment: classically activated macrophages (CAMs, M1-type macrophages) and alternatively activated macrophages (AAMs, M2-type macrophages) (Mehla and Singh 2019; Mackaness 1962; Liu et al. 2020). In general, M1 ϕ primarily functions to counteract early inflammation with danger signals, after which they tilt toward M2-like macrophages, whereas M2 ϕ primarily functions as immunomodulators rather than as efficient "killers" (Reiner 2009). M ϕ -EVs are important mediators not only in the pathology of various diseases (e.g., inflammatory diseases, fibrosis, and cancer), but also in immune regulation, cancer therapy, infectious defense, and tissue repair due to the nature of M ϕ . Furthermore, M1-EVs can repolarize M2 tumor-associated macrophages (TAM) to M1 ϕ , resulting in a pro-inflammatory microenvironment and enhancing the antitumor effects of checkpoint inhibitor treatment (Choo et al. 2018; Wang et al. 2021c).

There is evidence that loading drugs into macrophage-derived EVs to form EVs-drug complexes and then operating the complexes on tumor cells or tissues leads to improved tumor cell targeting, represents the fundamental building block for treating drug-resistant malignancies, and reduced tumor metastasis (Lou et al. 2022). Tian et al. (Tian et al. 2014) employed mouse immature dendritic cells (imDCs) to generate exosomes. ImDCs

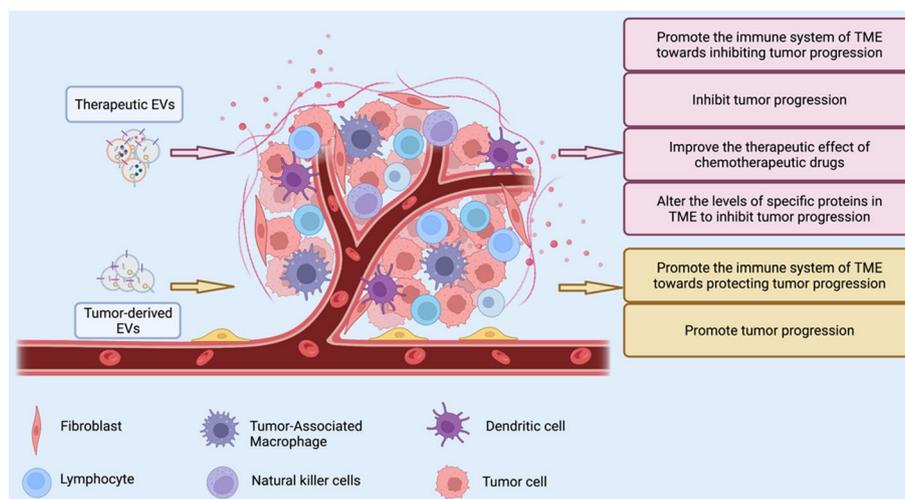


Fig. 3 Therapeutic extracellular vesicles (EVs) offer multiple advantages, such as enhancing the TME's immune system to inhibit tumor progression. They can efficiently deliver chemotherapeutic drugs into the TME, thereby increasing the therapeutic efficacy of these drugs. Moreover, they can regulate specific protein levels in the TME to suppress tumor progression and directly act on tumors to decelerate their growth. Conversely, tumor-derived EVs can stimulate the TME's immune system to promote tumor progression and alter factors within the TME that encourage tumor invasion and metastasis

were engineered to express a well-characterized exosomal membrane protein (Lamp2b) coupled to an iRGD peptide specific for αv integrin (CRGDKGPDC). The results indicate that iRGD exosomes efficiently target and transport doxorubicin (DOX) to αv integrin-positive breast cancer cells in vitro. Wang et al. (Wang et al. 2019) found that loading paclitaxel (PTX) onto M1EVs to form a PTX-M1EVs complex and administering it to a mouse breast cancer model not only transported PTX into the tumor tissue but also increased the drug's anticancer effects. Zhao et al. (Zhao et al. 2021) found that loading gemcitabine (GEM) and deferasirox (DFX, which improves the therapeutic efficacy of GEM sensitivity) onto M1EVs formed a GEM-DFX-M1EVs complex, which greatly increased the beneficial impact on GEM-resistant PANC-1/GEM cells and 3D tumor spheroids. Wang et al. (2022) loaded the hydrophilic hypoxia-activating prodrug AQ4N (A) into the inner core of M1EVs after functionalizing the membranes with two hydrophobic agents (chemical excitation source CPPO(C) and photosensitizer Ce6(C)). And loaded the hydrophilic hypoxia-activating prodrug AQ4N (A) into the inner core of M1EVs to form the CCA- M1EVs complex, which was found to have a powerful therapeutic effect in Glioblastoma multiforme. Jorquera-Cordero et al. (2022) pretreated M1 with hyaluronic acid (HA) and the β -blocker carvedilol (CV) and then obtained the treated EVs of M1. The resulting MM1EVs, on which DOX was further loaded to form DOX-MM1EVs, were found to enhance the therapeutic effect of the complex against metastatic tumors and the antitumor effect of DOX was enhanced by the synergistic effect of HA and CV. Kim et al. (2016) extracted RAW 264.7 cell-derived exosomes (EXOs), loaded with the anticancer drug PTX to obtain EXOs-PTX complexes, and applied the complexes to a mouse lung metastatic cancer model, which showed high anticancer efficacy. Subsequently, Kim et al. (2018) further optimized this novel nanoformulation based on this by incorporating amino acetamide-polyethylene glycol (AA-PEG) carrier molecules to target the sigma receptors overexpressed by lung cancer cells. The resulting AA-PEG-EXOs-PTX complex with high loading capacity improved the tumor therapeutic efficacy. Li et al. (2020) developed an M ϕ -EVs-encapsulated poly (lactic acid-ethanolic acid) nano platform for a DOX-targeting carrier in Triple-negative breast cancer (TNBC). The results showed that the nanocarrier significantly improved the efficiency of cellular drug cellular uptake, significantly increased tumor targeting efficacy, enhanced inhibition of tumor growth, and induced strong apoptosis of the tumor. Rayamajhi et al. (2019) used sEVs to hybridize with manufactured liposomes to create hybrid exosomes (HE) smaller than 200 nm in size. DOX was then loaded into HE and the drug-loaded HE was found to be more toxic to cancer cells. These findings point to M ϕ -EVs as a promising drug delivery strategy for tumor therapy.

Allogeneic EVs obtained from immune cells or tumors act on tumors to stimulate antigen presentation and T cells in vivo, resulting in the improved antitumor activity of T cells (Xu et al. 2020; Shi et al. 2020), making M ϕ -EVs a viable option for tumor vaccines. Certain macrophage-released factors (e.g., insulin-like growth factor, IGF-1) can play an important role in vaccine-induced immune responses by regulating immune cell homeostasis (Yoon et al. 2017). M1EVs can also cause a shift in TAMs from anti-inflammatory M2-like to pro-inflammatory M1-like. Seena et al. (Jean-Toussaint et al. 2021; McDonald et al. 2014) stimulated RAW 264.7 cells with lipopolysaccharide (LPS), collected their secreted sEVs, and prophylactically acted on neuronal cells and animal

models, observing the downregulation of pro-inflammatory target genes, which aided in the reduction of chronic pain. Cheng et al. (2017) prophylactically administered a peptide vaccine combined with M1EVs subcutaneously in a melanoma animal model and induced a stronger and more sustained immune response, showing the peptide vaccine induced a stronger and longer-lasting immune response in a melanoma animal model, demonstrating stronger anti-tumor effects. Tumor vaccines can overcome tumor-induced immunosuppression, enhance immunogenicity, activate the patient's immune system, and induce cellular and humoral immune responses in the body. It is worth mentioning that tumor vaccines usually need to be used in combination with other therapies or adjuvants to improve the extent, breadth, quality, and longevity of the vaccine immune response (Finn 2008). The roles of M ϕ -derived EVs in tumors are summarized in Table 1.

As mentioned above, Macrophage-derived EVs show great promise for applications that can easily evade immunological surveillance, have the ability to enhance or suppress immune activity, and may somewhat reduce some of the risks associated with whole cell therapy (Schulert and Grom 2015). In addition, compared to M ϕ , EVs are nanoscale, can remain in circulation for a long time and cross the biological barrier, enough to provide tumor suppression with the same targeting and intrinsic function. All described strategies demonstrate the design of M ϕ -EVs through different technical approaches to further enhance their potential application in cancer therapy. As we had hypothesized, these nanoparticles exhibit excellent adaptability to various modification processes, thus showing great versatility. However, after realizing the pathogenicity of M ϕ -EVs in disease, further study is necessary to figure out how to appropriately regulate their release or their embedded content to prevent the development and progression of disease. Moreover, macrophages are able to react differently to various microenvironments, a characteristic that seems to be important for their potent therapeutic effects in disease. However, unlike whole-cell therapy, M ϕ -EVs alone do not have similar effects, necessitating precise M ϕ -EV property modulation for various diseases or conditions prior to intervention. Since reprogramming or reconstituting M ϕ -EVs for disease treatment seems promising and the low yield and/or limited functionality of M ϕ -EVs using conventional methods, there is an urgent need for new isolation or manufacturing methods that enable higher yield/functionality of EVs. Overall, the potential of macrophage-derived EVs for immunomodulation and disease intervention is quite promising.

Mesenchymal stem cells-derived EVs

MSCs, discovered about 40 years ago (Friedenstein et al. 1970), are self-renewing cells found in various tissues (Murphy et al. 2013). They can be isolated from the umbilical cord, cord blood, adipose, placenta, dental pulp, and spinal cord tissues (Rezaie et al. 2022). MSCs are pluripotent cells that can differentiate into adipocytes, myocytes, osteocytes, and chondrocytes (Zuk et al. 2001; Minguell et al. 2001; Nombela-Arrieta et al. 2011). MSCs have a unique immunophenotypic capacity, tissue repair capacity, immunomodulatory capacity, and homing capacity to cross multiple biological barriers (Wang et al. 2014a; Ankrum et al. 2014). Furthermore, based on the paracrine fusion of MSCs with target cells, their mechanism of action was first shown to be enhanced by the cooperation of soluble bioactive factors, such as cytokines and growth factors. However,

Table 1 M ϕ -derived EVs in tumors

Source	Therapeutic agent	Targeting tumors/cells	Research models	Tumor cell lines	Outcomes	References
ImDCs	DOX	Breast cancer	In vivo/in vitro	MDA-MB-231 and MCF-7	Increased targeting and delivery of chemotherapeutic agents	Tian et al. (2014)
M1 ϕ	PTX	Breast cancer	In vivo/in vitro	4T1	Increased anti-tumor activity of the drug	Wang et al. (2019)
M1 ϕ	GEM and DFX	Pancreatic cancer	In vivo/in vitro	PANC-1	Inhibited cancer cell proliferation, cell attachment and migration, and chemoresistance to GEM significantly improved therapeutic efficacy	Zhao et al. (2021)
M1 ϕ	CPPO, Ce6 and AQ4N	Glioblastoma multiforme	In vivo/in vitro	U87MG-luc, GL261-luc, and G422-luc	Achieved a strong therapeutic effect with synergistic immunomodulation, CDT and hypoxia-activated chemotherapy	Wang et al. (2022)
RAW 264.7 cell	HA, CV and DOX	Breast Cancer	In vivo/in vitro	4T1	Reduced macrophage polarization regulation and cell migration enhance the therapeutic effect on metastatic cancer	Jorquera-Cordero et al. (2022)
RAW 264.7 cell	PTX	Lewis lung carcinoma	In vivo/in vitro	3LL-M27	Increased toxicity to cancer cells and localization to tumors	Kim et al. (2016)
RAW 264.7 cell	AA-PEG and PTX	Lewis lung carcinoma	In vivo/in vitro	3LL-M27	Increased toxicity to cancer cells and localization to tumors	Kim et al. (2018)

Table 1 (continued)

Source	Therapeutic agent	Targeting tumors/cells	Research models	Tumor cell lines	Outcomes	References
M1φ	lactic acid-ethanolic acid and DOX	TNBC	In vivo/in vitro	MDA-MB-231	Increased cellular uptake efficiency and antitumor efficacy of adriamycin, leading to increased tumor growth inhibition and induction of apoptosis	Li et al. (2020)
RAW 264.7 cell	DOX	Breast cancer	In vitro	4T1	Enhanced toxicity to cancer cells	Fu et al. (2015)
RAW 264.7 cell	–	Mouse cortical neurons, microglia and astrocytes	In vivo/in vitro	CCL-131	Downregulated pro-inflammatory miRNA target genes in receptor cells to prophylactically reduce chronic pain	Jean-Toussaint et al. (2021), McDonald et al. (2014)
M1φ	–	Melanoma	In vivo/in vitro	B16F10	Increased pro-inflammatory cytokine ratios induced stronger and more sustained immune responses, and exhibited stronger anti-tumor effects	Cheng et al. (2017)

“–”: EVs used alone, not loaded with therapeutic agents

shortly thereafter, it was found that the amplification of their mechanism of action in the context of secretion was dependent on their EVs (Meldolesi 2022).

MSCs-EVs have been shown to play an important role in cancer development, but their role in tumors remains controversial due to their heterogeneity or the status of the cancers they affect. EVs derived from MSCs isolated from human bone marrow (BM) increase the expression of VEGF in gastric cancer cells, promoting the growth of gastric cancer in vivo (Zhu et al. 2012). BM-MSCs-EVs from patients with multiple myeloma (MM) contains higher levels of oncogenic proteins, cytokines, and adhesion factors, all promoting tumor growth (Roccaro et al. 2013). BM-MSCs-EVs were also found to inhibit proliferation and promote apoptosis in hepatocellular carcinoma, Kaposi's sarcoma, and ovarian tumor cell lines (Bruno et al. 2013). EVs derived from MSCs isolated from human umbilical cords (UC) were found to induce drug resistance in gastric cancer cells through activation of the CaM-Ks/Raf/MEK/ERK pathway in both in vivo and in vitro experiments (Ji et al. 2015). EVs derived from human umbilical cord Wharton's jelly MSCs (hWJ-MSCs) may reverse the development of bladder cancer cells by down-regulating phosphorylation of Akt protein kinase and upregulating cleaved caspase-3

(Wu et al. 2013). EVs derived from adipose tissue (AT)-derived MSCs were shown to reduce Bcl-xL activity, promote apoptosis through the caspase-3/7 pathway, and inhibit prostate cancer by delivering miR-145 (Takahara et al. 2016). BM-MSCs-EVs and UC-MSCs-EVs reduced tumor cell proliferation and induced apoptosis in cancer cells in the U87MG glioblastoma cell line, whereas AT-MSCs-EVs promoted cancer cell proliferation (Fattore et al. 2015). As MSC culture conditions may affect the overall characteristics of the secreted vesicles, The inconsistency between these results suggests that more studies are needed to develop a personalized MSC culture condition.

MSCs also have great potential as drug carriers. Del Fattore et al. (2015) delivered vincristine (VCR) to UC-MSCs-EVs in a glioblastoma cell line and found increased cytotoxicity to cancer cells compared to free drug and unmodified EVs. Pascucci et al. (2014) pretreated MSCs with PTX and found that MSCs released increased MVs and expressed strong antiproliferative activity on the human pancreatic cancer cell line CFPAC-1. Munoz et al. (2013) discovered that MSC-derived exosomes loaded with anti-miR-9 reversed the expression of multidrug transporter proteins in drug-resistant glioblastoma multiforme cells and reversed chemoresistance. Katakowski et al. (2013) injected MSCs-EVs expressing miR-146b into a rat brain tumor model and found that tumor cell growth, migration, and invasion were inhibited, greatly reducing the development of glioma xenografts. Shimbo et al. (2014) delivered MSCs-EVs encapsulated with miR-143 to osteosarcoma cells, which significantly reduced the migration of osteosarcoma cells. Lou et al. (2015) transfected miR-122 into AT-MSCs and isolated EVs delivered miR-122 into hepatocellular tumor cells, which enhanced the sensitivity of tumor cells to chemotherapeutic agents in vitro and in vivo through the alternation of gene expression and tumor proliferation. O'Brien et al. (2018) subjected MSCs-EVs encapsulated with miR-379 to breast cancer and discovered that breast cancer progression was significantly inhibited in vivo. Li and Wu (2023) delivered MSCs-EVs encapsulated with miR-598 to straight non-small cell lung cancer (NSCLC) and showed that proliferation and migration of NSCLC cells were inhibited in vivo and in vitro. In a mouse model of pancreatic cancer, Kamerkar et al. (2017) found that electroporated MSCs exosomes with siRNAs targeting oncogenic KRAS inhibited cancer progression and significantly improved overall survival. Bliss et al. (2016) found that breast cancer cells prompted MSCs to secrete exosomes with the characteristics of specific miRNAs, such as miR222/223, thereby reducing the therapeutic effect. Based on this discovery, MSCs encapsulated with antagomiR-222/223 were designed and applied to breast cancer cells to put them into dormancy, resulting in improved chemotherapy sensitivity and survival. The roles of MSCs-derived EVs in tumors are summarized in Table 2.

In conclusion, these findings demonstrate that MSCs-EVs has the potential to be effective in drug and/or nucleic acid delivery. Moreover, MSCs are a promising nanocarrier due to their superiority in large-scale EV production, clinical applicability (Yeo et al. 2013), and their safety profile. However, since the role of MSCs is still controversial and different MSCs may produce different EVs that are different in size and function, we need to select the appropriate MSCs for different tumors. In addition, cancer stem cells (CSCs) are also widely present in the ecological niche and are closely related to cancer progression (Kim et al. 2021; Pan et al. 2017), so targeting CSCs-EVs while searching for a new therapeutic modality would be an innovative approach.

Table 2 MSCs-derived EVs in tumor

Result	Source	Therapeutic agent	Targeting tumors/cells	Research models	Tumor cell lines	Outcomes	References
Tumor promotion	BM	–	Gastric Cancer	In vivo/in vitro	SGC-7901 and SW480	Stimulation of tumor angiogenesis by activation of ERK1/2 and p38 mitogen-activated protein kinase pathway induced by VEGF expression	Zhu et al. (2012)
	MIMBM	–	MM	In vivo/in vitro	MM.1S, RPMI.8226, and U266	Supported tumor progression by transfer of lower amounts of the exosomal tumor suppressor miR-15a	Roccaro et al. (2013)
	UC	–	Gastric Cancer	In vivo/in vitro	HGC-27, MGC-803, and SGC-7901	Induced drug resistance in gastric cancer cells by activation of CaM-Ks/Raf/MEK/ERK pathway	Ji et al. (2015)
	AT	–	Glioblastoma	In vitro	U87MG	Promoted the proliferation of cancer cells	Fattore et al. (2015)
Tumor inhibition	BM	–	Hepatocellular carcinoma, Kaposi's sarcoma and ovarian tumors	In vivo/in vitro	HepG2, Skov-3, and Kaposi's sarcoma cell lines	Inhibited tumor growth	Bruno et al. (2013)
	UC Wharton's jelly MSCs	–	Bladder cancer	In vivo/in vitro	T24	Inhibited tumor growth by down-regulating phosphorylation of Akt protein kinase and up-regulated cleaved cystathionine-3	Wu et al. (2013)
	AT	–	Prostate cancer	In vivo/in vitro	PC3M-luc2	Inhibited tumor growth by shifting miR-145 to reduce Bcl-XL activity and promoted apoptosis via the cystatin-3/7 pathway	Takahara et al. (2016)

Table 2 (continued)

Result	Source	Therapeutic agent	Targeting tumors/cells	Research models	Tumor cell lines	Outcomes	References
	BM and UC	–	Glioblastoma	In vitro	U87MG	Inhibited tumor cell proliferation and promoted tumor cell apoptosis	Fattore et al. (2015)
	UC	PTX	Glioblastoma	In vitro	U87MG	Increased cytotoxicity to tumor cells	Fattore et al. (2015)
	MSCs	PTX	Pancreatic cancer	In vitro	CFPAC-1	Inhibited tumor cell proliferation	Pascucci et al. (2014)
	MSCs	Anti-miR-9	Glioblastoma multiforme	In vitro	U87, T98G, BT145, and BT164	Reversed expression of multidrug transporter proteins and reversed chemotherapy resistance	Munoz et al. (2013)
	MSCs	miR146b	Glioma	In vivo/in vitro	Glioma cells	Inhibited glioma xenograft progression in a brain tumor model	Katakowski et al. (2013)
	MSCs	miR-143	Osteosarcoma	In vitro	143B	Inhibited osteosarcoma migration	Shimbo et al. (2014)
	MSCs	miR122	Hepatocellular carcinoma	In vivo/in vitro	HepG2	Increased sensitivity of tumor cells to chemotherapeutic agents and tumor growth	Lou et al. (2015)
	MSCs	miR-379	Breast cancer	In vivo/in vitro	T47D and HCC-1954	Inhibited the progression of breast cancer	O'Brien et al. (2018)
	MSCs	miR-598	NSCLC	In vivo/in vitro	H1299, A549, H522, and H460	Inhibited the promotion of proliferation, migration and invasion of NSCLC cells by THBS2	Li and Wu (2023)
	Human foreskin fibroblast-like/MSCs	siRNA for oncogenic Kras	Pancreatic Cancer	In vivo	Capan-1, MIA PaCa-2, BxPC-3, and T3M4	Inhibited cancer progression and improved overall survival	Kamerkar et al. (2017)
	MSCs	antagomiR-222/22	Breast Cancer	In vivo/in vitro	MDA-MB-231 and T47D	Lead breast cancer dormant and improved chemotherapy sensitivity and survival	Bliss et al. (2016)

“–”: EVs used alone, not loaded with therapeutic agents

Milk-derived EVs

Milk is a complex fluid with multiple immunoreactive capabilities of cells and soluble proteins that provide immunity and influence the immune system (Cacho and Lawrence 2017), and milk-derived EVs (MEVs) have also been shown to have the ability to influence the immune response (Admyre et al. 2007; Sun et al. 2013; Nordgren et al. 2019). Furthermore, EVs from different dairy products have similar bidirectional immunomodulatory effects as raw milk EVs, not only promoting normal macrophage proliferation, increasing NO and cytokine (IL-1 β , IL-6, and TNF- α) levels, and regulating immune-related miRNAs, but also inhibiting the LPS-induced TLR4/NF- κ B pathway and inflammatory cytokines (Li et al. 2022).

Milk-derived EVs were found to reduce primary tumor growth in mouse models of colon and breast cancer, but milk-derived EVs accelerated tumor metastasis in mouse models of breast and pancreatic cancer, suggesting that milk-derived EVs (at reasonable concentrations or for reasonable periods) can be used for tumor therapy judiciously (Samuel et al. 2021). Curcumin has limited pharmaceutical use despite its many bioactive and therapeutic properties due to its poor water solubility, stability, and low systemic bioavailability. Curcumin loading onto milk EVs acting on a human epithelial home rectal adenocarcinoma cell line (Caco-2) revealed that encapsulating curcumin into EVs improved its stability, solubility, and bioavailability (Vashisht et al. 2017). He et al. (2022) addressed the problem of immature nanofabrication and inadequate bioavailability of chiral nanostructures, and the chiral peptide Au(I) infinite covalent polymer (DPAICP) was camouflaged using MEVs feasible camouflage technology to construct a complex with good drug properties in the B16F10 homozygous malignant melanoma model, LLC Lewis orthotopic transplantation lung cancer model and patient-derived orthotopic xenograft (PDOX) colon cancer mouse model to restore the p53 signaling pathway for cancer treatment. In addition, oral administration of the complex further activated T cells and enhanced the effect of anti-PD1 immunotherapy. Multimodal image-guided photothermal therapy (PTT) has great potential for cancer treatment due to its low side effects and efficacy. Jing et al. (2023) designed a therapeutic nanoprobe for positron emission tomography/computed tomography/near-infrared fluorescence (PET/CT/NIRF) imaging and image-guided photothermal therapy (PTT) for colon cancer by taking the anti-inflammatory ability and tumor-sparing ability of goat milk-derived EVs (GEVs). Compared with indocyanine green (ICG) mediated PTT, PTT mediated by GEVs/ICG nanoprobe triggered stronger anti-tumor immune and inflammatory responses. In addition, nanoprobe can attenuate PTT-induced inflammation due to the anti-inflammatory efficacy of GMVs. The roles of milk-derived EVs in tumors are summarized in Table 3.

Milk can be a source for harvesting large amounts of EVs due to its biocompatibility and cost-effective potential, and MEVs have great potential as drug carriers for hydrophilic and lipophilic drugs, including chemotherapeutic drugs. This nanodevice technology could overcome the limitations associated with low oral bioavailability of chemopreventive and chemotherapeutic drugs and reduce the total administered dose, thereby minimizing or eliminating the toxicity generally associated with high doses. MEVs formulation of drugs not only improves biological efficacy but targeting tumors with ligand-functionalized MEVs can further improve specificity and eliminate off-target

Table 3 Milk-derived EVs in tumor

Source	Therapeutic agent	Targeting tumors/cells	Research models	Tumor cell lines	Outcomes	References
Milk	–	Colon cancer and breast cancer	In vivo/in vitro	4T1.2, LIM1215 and MCF7	Induced the senescence of tumor cells and reduced the primary tumor load in the body, but increased the metastasis of tumors	Samuel et al. (2021)
Milk	Curcumin	Colon adenocarcinoma	In vitro	Caco-2	Increased stability, solubility and bioavailability of curcumin	Vashisht et al. (2017)
Turing milk	DPAICP	Malignant melanoma, lung cancer and colon cancer	In vivo	–	Restored the p53 signaling pathway, further activating T cells and enhanced anti-PD1 immunotherapy	He et al. (2022)
Goat milk	PTT and ICG	Colon Cancer	In vivo/in vitro	MC38	Triggered anti-tumor immune and inflammatory responses to enhance PTT	Jing et al. (2023)

“–”: EVs used alone, not loaded with therapeutic agents

side effects of the drug. The multiple properties of MEVs, such as physical and biological stability, tolerability, scalability of manufacturing processes, versatility in the drugs they can carry, and the ability to functionalize with ligands, make them ideal candidates for drug delivery with a wide range of therapeutic uses. However, further studies are needed to rule out the potential toxicity of the long-term use of MEVs.

Plant-derived EVs

Plant-derived EVs (PDEVs) are biologically and morphologically similar to mammalian-derived EVs (MDEVs) (An et al. 2007) but have different nucleic acid, lipid, and protein contents compared to mammalian EVs (Zhang et al. 2016a; Alfieri et al. 2021), and sometimes contain plant-specific specific chemical components associated with plants (Ji et al. 2016; Cui et al. 2020). PDEVs can be isolated from the sap of plants (Zhao et al. 2018; Pocsfalvi et al. 2018; Xiao et al. 2018) and the pulp or roots of plants (Teng et al. 2018; Wang et al. 2013; Zhuang et al. 2015). In addition, EVs can be isolated from the seeds of plants (Regente et al. 2009) and dried plant material (Woith and Melzig 2019). PDEVs are highly stable under various environmental conditions, are enriched with enzymes essential for cell wall remodeling and proteins with antifungal and antibacterial properties (Canal and Pinedo 2018; Liu et al. 2021; Regente et al. 2017; Rutter and Innes 2018), and are resistant to degradation by certain digestive enzymes (Akuma et al.

2019). The suitability of PDEVs as alternatives to MDEVs is currently being investigated, allowing researchers to circumvent the technical limitations of MDEVs. In terms of their large-scale production, PDEVs have great potential for applications in disease treatment and in the development of nanocarrier DDS capable of administering various doses due to their physiological, chemical, and biological properties (Zhang et al. 2016a; Yang et al. 2018; Rome 2019; Jimenez-Jimenez et al. 2019). Due to these beneficial properties, PDEVs outperform mammalian EVs in terms of therapeutic efficacy.

Phytochemicals are effective in inhibiting tumor proliferation (Abu-Dahab et al. 2014; Fiore et al. 2006), and PDEVs, to some extent, share this property. It has been shown that PDEVs can alter immune regulation in terms of the tumor microenvironment, including macrophages (Wang et al. 2014b; Mu et al. 2014), and that PDEVs play an important role in the treatment of inflammation (Zhuang et al. 2015; Zhang et al. 2017) and tumors (Robertis et al. 2020; Chen et al. 2022b). A population of nanovesicles isolated from Citrus fruit exhibited a strong inhibitory effect on chronic granulocytic leukemia (CML) by inhibiting angiogenesis and TRAIL-mediated apoptosis (Raimondo et al. 2015). Lemon-derived EVs (LDEVs) elevates the level of GADD45a, leading to S-phase arrest and apoptosis in gastric cancer cells, thereby inhibiting gastric cancer progression (Yang et al. 2020). Apple-derived NPs (APNPs) affect intestinal transport proteins as well as human Caco-2 cells (Fujita et al. 2018). EVs derived from hairy root (HR) cultures obtained from *Salvia dominica* exhibit selective and potent pro-apoptotic activity against pancreatic and breast cancer cells (Boccia et al. 2022). Cannabidiol-derived EVs (CBDEVs) caused G0/G1 phase arrest in the hepatocellular carcinoma cell cycle and significantly induced cell death in the hepatocellular carcinoma cell lines HepG2 and Huh-7 cells by activating the mitochondria-dependent apoptotic signaling pathway (Tajik et al. 2022). EVs derived from *Dendropanax morbifera* and *Pinus densiflora* have cytotoxic effects on breast and skin tumor cells, and the combination of both can increase the toxic effects to some extent (Kim et al. 2020). Tea leaf-derived EVs (TLEVs) can increase ROS levels in breast cancer cell lines, trigger mitochondrial damage in tumor cells and block the cell cycle, causing tumor cell apoptosis and thus slowing tumor growth (Chen et al. 2023). Ginseng-derived nanoparticles (GDNPs) can alter TLR4 and MyD88 signaling thereby altering M2 macrophage polarization, thereby inhibiting melanoma growth (Cao et al. 2019).

The specificity of plant-derived exosomes given by specific orientations and their ability to manipulate genes for treatment, transfer hydrophobic drugs, and escape immune attacks, make them suitable for collaboration for future medical applications in DDS (Cong et al. 2022). Drug-targeting systems using PDEVs as carriers enable efficient targeted drug delivery. Exogenous bovine serum albumin (BSA) and heat shock protein (HSP70) were delivered to human peripheral blood mononuclear cells and colon cancer cells after loading on grapefruit-derived extracellular vesicles (GEEVs), revealing that protein-loaded PDEVs significantly improved exogenous protein uptake by human cells compared to the same proteins without EVs (Garaeva et al. 2021). Ginger-derived EVs (GDEVs) and folic acid (FA), a small molecule ligand that can bring nanoparticles into cells within 15–30 min via a receptor-mediated endocytic pathway. A complex is formed, exogenous surviving protein siRNA is loaded onto the complex, and the siRNA-FA-3WJ-GDEVs complex is intravenously delivered to the tumor. Inhibition of tumor growth was observed on a xenograft model, promoting apoptosis of tumor tissue cells

and significantly reducing tumor weight (Li et al. 2018). It was also found that GDENs lacking FA modification was much far likely to be taken up by cancer cells in vivo compared to FA-modified GDENs (Li et al. 2018). Besides, PDEVs can alleviate intestinal inflammation and have great potential in the treatment of inflammatory bowel disease (IBD) and colitis-associated cancer (CAC). DOX was loaded on FA-modified ginger-derived nanocarriers (GDNVs) to form DOX-FA-GDNVs complexes for targeted delivery to Colon-26 tumors. The results showed enhanced inhibition of tumor growth compared to the free drug (Zhang et al. 2016b). The roles of plant-derived EVs in tumors are summarized in Table 4.

PDNVs can deliver nucleic acids and drugs, are more biocompatible than synthetic carriers and can be mass-produced, making them attractive for pharmaceutical applications in the medical field. However, the limitations of PDEVs are their unknown mechanism of uptake action and the many biomolecules that may cause side effects due to the versatility of these components. Little is known about plant-derived EVs and their function, origin, formation, and secretion have not been thoroughly studied (An et al. 2007; Borges and Martienssen 2015). Although it has been established that PDEVs are first transported to the liver and other organs after uptake (Gioia et al. 2020; Deng et al. 2017), the mechanisms of vesicular uptake of plant-derived EVs by mammalian cells are clathrin-mediated endocytosis, phagocytosis, macropinocytosis, and plasma or endosomal membrane fusion of EVs (Zhuang et al. 2015). However, the findings of these studies only explain a portion of the pathways by which PDEVs enter mammalian cells, and much more research is needed to better understand the therapeutic potential of PDEVs. Another unanswered question is whether any fraction derived from plants can be considered equivalent. We don't know if nanoparticles from roots, stems/stalks, or leaves make a difference, or if they do, so this is an issue that deserves attention in future studies. The pharmacokinetics, pharmacodynamics and safety of PDEVs in a wide range of animal disease models also need to be explored further. Overall, although phytochemicals are effective in inhibiting tumor proliferation, the application of PDNVs in these areas is still empirical and further experiments on the stability and function of PDEVs in various settings are still needed, and this information may help to better understand the future application of PDEVs in therapy.

Summary

In summary, extracellular vesicles (EVs) possess a range of unique properties and play crucial roles in various biological processes such as angiogenesis, apoptosis, cellular homeostasis maintenance, antigen delivery, inflammatory responses, and intercellular signaling. These attributes render them highly promising for oncological disease applications. Their multiple unique properties make them particularly advantageous for tumor diagnosis and treatment. Nevertheless, it is important to note that these very properties also present challenges for EV application. Among the EVs currently under study, macrophage-derived EVs can evade immune surveillance and exhibit potent immune activity, making them highly effective in tumor therapy. However, their low yield and limited functionality render them unsuitable for large-scale production. While mesenchymal stem cell (MSC)-derived EVs, milk-derived EVs, and plant-derived EVs can be produced on a larger scale and possess distinct properties, they are not yet well understood, and

Table 4 Plant-derived EVs in tumor

Source	Therapeutic agent	Targeting tumors/cells	Research models	Tumor cell lines	Outcomes	References
Citrus fruit	–	CML	In vivo/in vitro	LAMA84	Inhibited angiogenesis and TRAIL-mediated apoptosis and showed strong inhibitory effects in CML	Raimondo et al. (2015)
Lemon	–	Gastric cancer	In vitro	AGS, BGC-823, and SGC-7901	Elevated levels of Ie GADD45a lead to tumor cell cycle S-phase arrest and apoptosis, thereby inhibiting tumor progression	Yang et al. (2020)
Apple	–	Colorectal adenocarcinoma	In vitro	Caco-2	Altered function of intestinal transporter proteins	Fujita et al. (2018)
HR obtained by <i>Salvia dominica</i>	–	Pancreatic Cancer and breast cancer	In vitro	MIA PaCa-2 and MCF-7	Promoted apoptosis of cancer cells	Boccia et al. (2022)
Cannabidiol	–	Hepatocellular carcinoma	In vitro	HepG2 and Huh-7	Induced G0/G1 phase arrest in the cell cycle of cancer cells and induced cancer cell death by activating the mitochondria-dependent apoptotic signaling pathway	Tajik et al. (2022)
<i>Dendropanax morbifera</i> , <i>Pinus densiflora</i>	–	Breast cancer and skin tumor	In vitro	A431, MCF7, and MDA-MB-231	Promoted cytotoxicity	Kim et al. (2020)
Tea leaves	–	Breast cancer	In vitro	MCF7 and 4T1	Increased ROS levels in breast cancer cell lines triggered mitochondrial damage in tumor cells and blocked the cell cycle, leading to apoptosis and thus retarding tumor growth	Chen et al. (2023)

Table 4 (continued)

Source	Therapeutic agent	Targeting tumors/cells	Research models	Tumor cell lines	Outcomes	References
Ginseng	–	Melanoma	In vivo/in vitro	B16F10	Altered TLR4 and MyD88 signaling thereby altering M2 macrophage polarization, inhibiting melanoma growth	Cao et al. (2019)
Grapefruit	BSA and HSP70	Colon cancer	In vitro	HCT116 and DLD1	Improved uptake of exogenous proteins by human cells	Garaeva et al. (2021)
Ginger	FA and surviving protein siRNAs	KB cell derived xenograft models	In vivo/in vitro	KB	Expanded the drug activity of siRNA and inhibited tumor growth	Li et al. (2018)
Ginger	FA and DOX	IBD and CAC	In vivo/in vitro	HT-29, Caco2-BBE, and colon 26 cells	Expanded the drug activity of chemotherapeutic drugs and enhanced tumor suppression	Zhang et al. (2016b)

“–”: EVs used alone, not loaded with therapeutic agents

outcomes vary depending on the source. In conclusion, despite their vast potential in oncology therapy, EVs face several challenges that need to be addressed. Technological advancements are expected to resolve these issues in the future. A comprehensive overview of the advantages and disadvantages of EVs in the context of tumor therapy development is provided in Table 5.

Discussion and prospects

Cancer is a significant burden in all countries, and it is rising with economic growth. However, there are currently no effective therapeutic approaches. Intercellular communication is critical for maintaining homeostasis in vivo in single cells and multicellular organs, and EVs contain a variety of molecules of communication substances with multiple benefits that have a significant impact on cancer cell communication with local cells and distant organs, participating in many physiological and pathological pathways. This makes it possible to explore new approaches through EVs for safe and effective treatment. The ability of M ϕ -EVs to exploit the characteristics of donor cells, such as convergent chemotaxis toward inflammatory tissues and tumor sites via macrophagic features, helps to achieve personalized and effective anti-cancer therapy. In addition to this, allogeneic exosomes derived from macrophages or tumors allow us to harvest tumor vaccines. MSCs are easily obtainable, and MSC-EVs have properties such as low immunogenicity and high biocompatibility, as well as the ability to be efficiently modified to selectively reach target tissues. MEVs preserve the bioactive

Table 5 Advantages and disadvantages of EVs in tumor therapy

Category	Advantages	Disadvantages	References
EVs	Biocompatibility Low immunogenicity Minimized size Rich in surface proteins Long dwell time High shuttling ability Low clearance rate Accurate localization Can be degraded and recovered in vivo Higher safety profile Improved drug stability and bioavailability	Inefficient extraction and purification methods High costs Difficult preservation methods Difficult preservation methods Uncertain delivery methods Uncertain pharmacokinetics Uncertainty of optimal safe dose Uncertain mechanism of action Immaturity of nanotechnology Lack of clinical trials	Lerch et al. (2013), Mitchell et al. (2021), Jeon et al. (2018), Dai et al. (2019), Qiao et al. (2020), Betzer et al. (2017), Shahjin et al. (2020), Skotland et al. (2017), Polanco et al. (2021), Abello et al. (2019), Belhadj et al. (2020), Fu et al. (2021), Zhang et al. (2020), Walker et al. (2019), Lin et al. (2019)
Macrophage-derived EVs	Avoidance of immune surveillance Modulates immune activity Reduces risk of whole cell therapy	Low yield Limited functionality on its own	Wang et al. (2021c), Lou et al. (2022), Schulert and Grom (2015)
MSCs-derived EVs	Large-scale production Regulates immune activity Regenerative	Uncertain source Uncertain results	Wang et al. (2014a), Ankrum et al. (2014), Meldolesi (2022), Yeo et al. (2013)
Milk-derived EVs	Large-scale production Regulates immune activity Hydrophilic and lipophilic	Uncertain results	Admyre et al. (2007), Sun et al. (2013), Nordgren et al. (2019), Li et al. (2022)
Plant-derived EVs	Large-scale production High stability Antibacterial properties Resistant to degradation by digestive enzymes Contains phytospecific chemical components	Insufficient understanding Variable phytoconstituents Uncertain source	An et al. (2007), Alfieri et al. (2021), Ji et al. (2016), Cui et al. (2020), Canal and Pinedo (2018), Liu et al. (2021), Regente et al. (2017), Rutter and Innes (2018), Borges and Martienssen (2015)

molecules sequestered in milk, inherent properties that allow them to survive in harsh, degradable environments and to be distributed in peripheral tissues. This is encouraging evidence that the various cargoes carried by MEVs are epigenetically regulated in the receptor. Medicinal plants contain specific phytochemicals, proteins, and nucleic acids, making the study of PDEVs especially appealing given the variety and abundance of medicinal plants, as well as the advantage of being consistently isolated in large quantities. When these emerging EV technologies are combined, they will play a critical role in future oncology treatments. It's worth noting that one study discovered that delivering mouse self-derived EVs loaded with exogenous siRNA to the mouse brain was significantly effective in the treatment of Alzheimer's disease (Alvarez-Erviti et al. 2011). Is it possible to achieve promising results in tumor treatment by collecting and modifying self-derived EVs from patients? Is it also possible to combine the use of the aforementioned EVs with unexpected results? In conclusion, with appropriate modifications, these nanovesicles can be used for tumor therapy and antitumor drug development.

Emerging EVs technologies offer new therapeutic ideas for the treatment of cancer through metabolic reprogramming techniques. However, these nanotechnologies are increasingly being recognized as a complex, tightly regulated phenomenon that affects and/or is influenced by various characteristics of tumor cells and TMEs. Notably, we need to consider not only the complex regulation of metabolism by internal factors but also regulation by external factors, which frequently affect the efficacy of the treatment. Furthermore, We need to further optimize the standardized methods for large-scale isolation and purification because the current conventional methods of EV extraction and purification are ineffective. Finding the best source of EVs is important considering there is instability in the EV source and different EVs contain different cargoes. We need to identify methods that can quickly and accurately quantify and characterize EVs as preserving EVs is a challenging process. We also need to conduct more in-depth studies on the pharmacokinetics of EVs in vivo, safe and efficient methods of EVs delivery to the body or targeted therapeutic sites, and optimal doses for treating various diseases. The impact of genetic engineering techniques on EVs remain largely unknown, nanotechnology for cancer has not yet matured, and many studies have not yet been converted from experimental to clinical stages. Clarification of these key concerns would make EVs a more fantastic novel cell-free therapeutic strategy for the clinical treatment of tumors, factors that have largely impeded further biomedical applications. Certainly, EVs have a promising future. New techniques for EV isolation and purification are under study, high quality and easy storage technologies will emerge, the understanding and application of EVs will become clearer, and the application of nanotechnology will become more proficient and will provide more practical options for future exosome applications. In conclusion, the emerging EVs technology is a promising means of treating oncology, and we need a deeper understanding in order to address the challenges and opportunities presented by the rapidly evolving cancer nanotechnology and biology.

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Author contributions

HL conceived the manuscript, HL searched for publications and draft the manuscript. HL and JJ edited tables and figures. JJ, KL, HH, SF, FZ and JZ reviewed the manuscript and polished the grammar. All authors read and approved the final manuscript.

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