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REVIEW ARTICLE

Exosomes as Therapeutic Vehicles for Cancer

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Abstract

BACKGROUND: Exosomes are membrane-enclosed extracellular vesicles implicated in cell–cell communication. Exosomes contain proteins, mRNAs, non-coding RNAs (miRNAs and lncRNAs) and lipids that are derived from producing cells. These nano-sized vesicles are present in biofluids including blood, urine, saliva, amniotic fluid, semen and conditioned media of cultured cells.

METHODS: This review summarizes current progress on the strategies of development of diagnostic biomarkers and drug loading onto exosomes for overcoming cancer progression.

RESULTS: A number of studies indicate that the exosome appears to be a key player in tissue repair and regeneration of in a number of animal disease models. In addition, alterations of the molecular profiles in exosomes are known to be correlated with the disease progression including cancer, suggesting their usefulness in disease diagnosis and prognosis. Studies utilizing engineered exosomes either by chemical or biological methods have demonstrated promising results in a number of animal models with cancer.

CONCLUSION: Understanding the molecular and cellular properties of exosomes offer benefits for cancer diagnosis by liquid biopsy and for their application in therapeutic drug delivery systems. Studies have shown that genetic or molecular engineering of exosomes augmented their target specificity and anticancer activity with less toxicity. Thus, deeper understanding of exosome biology will facilitate their therapeutic potential as an innovative drug delivery system for cancer.

Keywords Exosomes · Drug delivery · Cancer · Extracellular vesicles · Target specificity

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1 Introduction

The key requirements for ideal drug delivery system (DDS) are safety, nontoxicity, efficiency, non-immunogenicity, bioavailability, and targeting ability. While a number of DDS, such as liposomes, micelles, nanoparticles and hydrogels, have been developed for the purpose of effective drug delivery [1], most of them faced two critical issues: high systemic toxicity and low bioavailability. The most recent addition to the fields of DDS is nano-sized extracellular vesicles, such as exosomes and microvesicles, that possess organotropism [2], good bioavailability with little toxicity and immunogenicity [3].

The exosomes and microvesicles are a relatively new addition to the complex avenue of the intercellular communication. Their existence was known for decades by electron microscopy from pellets from plasma ultracentrifugation [4]. The presence of exosomes in *in vitro* cultured cells and *in vivo* tumor ascites was first reported by Dvorak et al. [5] in 1981. Later, exosomes found to be produced by nearly all types of cells including immune cells [6, 7], epithelial cells [8], neurons [9], mesenchymal stem cells [10] and red blood cells [11]. In addition, they were identified in most bodily fluids including blood plasma [12], cerebrospinal fluid [13], urine and amniotic fluids [14], breast milk [15] and saliva [16].

Exosomes are membrane-enclosed nanosphere of 30–150 nm in diameter originated from a subset of late endosomes (also known as multivesicular bodies, MVBs) during ceramide-dependent initiation phase. Fusion of outer membrane of MVBs with plasma membrane releases the exosomes [17] that deliver cargo including soluble and membrane bound proteins, lipids, mRNAs, microRNAs and chemical messengers into extracellular space (Fig. 1). Reflecting their subcellular origin, exosomes contain a number of endosomal membrane proteins, proteins involved in exosome biogenesis [18], vesicle trafficking proteins and plasma membrane-associated proteins [19, 20]. Similar to lipid rafts, they are rich in cholesterol, glycosphingolipids, and phosphatidylserine [21] accounting for their higher stability and rigidity. In addition to these, exosomes cargo large amounts of nucleic acids, including mRNAs, microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) [22].

2 Physiological function of exosomes

These subcellular particles are ubiquitous and secreted by virtually all types of cells in our body. Upon fusion with by local or distant target cells, exosomes deliver complex sets of biological information to recipient cells thereby modulating their behaviors by their molecular cargo. While nomenclatures of exosomes, microvesicles and apoptotic bodies were based on their sources and sizes, the terms of exosome and microvesicle are confusing and often used interchangeably due to their overlapping sizes as well as sharing common markers. A number of different strategies have been developed to isolate and/or purify these extracellular vesicles from biofluids, including ultracentrifugation, size exclusion chromatography, density gradient centrifugation, immunoaffinity-mediated sorting, microfluidics and filtration [23–25]. Since these technologies cannot distinguish exosomes and microvesicles, the functional assignment and physiological significance of these particles is a challenging project. Due to the complexity of molecular cargo including proteins, nucleic acids and lipids, exosomes can deliver multiple biological information at once. To date, large number of

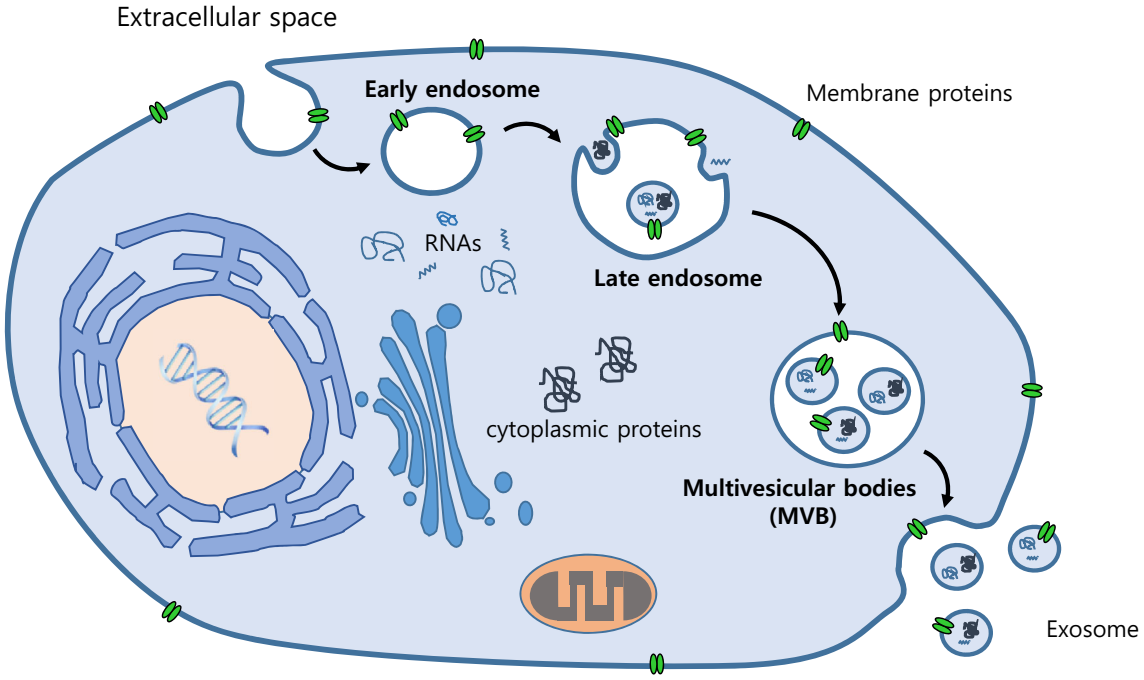

Fig. 1 Biogenesis of exosomes from multivesicular endosome. Exosomes formed by invagination of endosomal membrane are secreted vesicles derived from intraluminal vesicles within multivesicular body (MVB). Upon fusion of MVB with plasma membrane, exosomes carrying proteins, RNAs and lipids that are derived from donor cells are released the in the extracellular space

transcriptome and proteome analyses have been performed to elucidate the physiological function of exosomal components (many of them are cataloged in the ExoCarta database, www.exocarta.org) [26].

Exosomes are secreted from cells under change of physiological conditions by cell growth, cell injury, inflammation, hypoxia, oxidative stress and carcinogenesis [27]. For instances, exosomes is a potential mediator for development process through WNT and Hedgehog signaling that regulate cell proliferation and differentiation during embryonic development [28]. In addition, immune cells-derived exosomes accounts for a large population of circulating exosomes within blood [29]. Dendritic cells, a pivotal player of innate and adaptive immunity, are known to modulate T cell responses [30, 31] and natural killer (NK) cell function [32] via secreted exosomes. Exosomes derived from proinflammatory (M1-polarized) macrophages exhibited a trophism toward lymph nodes upon *in vivo* administration and induced strong cytotoxic T cell response [33] suggesting their potential use as an immunoadjuvant for cancer therapy.

Recently, exosomes are considered as novel biomarkers for diagnosis of early detection, chemoresistance, therapy response and poor prognosis leading to relapse in cancer research. Cancer-derived exosomes appears to play important roles in cancer initiation, promotion and progression by cell–cell communication [34] and thus exosomal biomarkers can serve as a potential indicator of real-time status of the disease progression. Based on the possibility to isolate exosomes from human body fluid, exosomal biomarkers have been widely investigated to screen progression of cancers with low-cost, short time, reduced pain by liquid biopsy [35]. Here, we will highlight and discuss the more recent issues related to molecular mechanisms of exosome in cancer development and the utilization of exosomes as DDS for their potential clinical applications.

3 Exosomes in cancer progression and diagnostics

Unlike normal physiology, the onset of cancer may alter the molecular cargo of exosomes, i.e., lipids, proteins, mRNAs, miRNAs and lncRNAs. Recently, exosomal RNAs have been widely reported in cancer progression with aspects of cell proliferation [36], migration [37], apoptosis, metastasis [38], angiogenesis [39], and chemoresistance [40]. The lncRNAs in cancer cells-derived exosomes regulates survival rates of the cells by transferring genetic information via cell-to-cell communication for mediating cancer microenvironment. In colon cancer, lncRNA H19 in cancerous cell-derived exosomes activates β-catenin signaling leading to cancer development and chemoresistance [41]. In addition, first identified lncRNA MALAT-1 related in lung cancer progression isolated from serum exosome stimulates cell proliferation and migration whereas it suppresses cell death of lung cancer cells [42]. Also, lncRNAs functions as an oncogene by increasing non-controlled proliferation of cancerous cells originated from liver, thyroid, bladder, lung and ovary [43–45]. For example, lncRNA FAL1 was upregulated in tumor tissues and serum exosomes from hepatocellular carcinoma (HCC) patients and the transfer of exosomal FAL1 to HCC cells increased their proliferative and migratory capacity which was mediated by competitive binding to miR-1236 [46]. Taken together, these studies suggest that exosomal lncRNAs regulate key cellular events, via epigenetic and transcriptional regulation, in tumor progression and metastasis.

For diagnosis of early stage cancers, it is important to develop an optimal biomarker. Although tissue biopsy has been commonly used for histopathological analysis, it is hard to use in cancer screening and determination of heterogeneous characteristics of cancers for therapy. In addition, the tissue biopsy has limitations in cost burden, invasive tissue collection, pains, and identification of genetic changes for monitoring therapy response and prognosis of cancers [47]. In order to overcome these limits, new approaches for detection of early diagnosis, chemoresistance, relapse and microenvironment of cancers are required in these days. Liquid biopsy has a variety of advantages of diagnosis, treatment and therapy response in cancer research based on genetic materials of exosomes and circulating tumor cells (Fig. 2) [35, 48]. Especially, analytical methods of exosomal genomic materials have been developed for cancer diagnosis and prevention (Table 1). For examples, serum exosomal expression of prostate cancer associated transcript 1 (PCAT-1), upregulated in bladder cancer 1 (UBC1), small nucleolar RNA host gene 16 (SNHG16), and H19 belonging to lncRNAs show high diagnostic accuracy for bladder cancer [49, 50]. In addition, exosomal miR-21, miR-105, miR-155, miR-301, and miR-1246 derived from the blood of breast cancer patients can be used as biomarkers to predict the progression of malignancy and metastasis [51–53]. In colorectal cancer patients resistant to treatment with cetuximab, the expression of urothelial carcinoma-associated 1 (UCA1), the lncRNAs, is high in serum exosome [54]. Diagnosis of esophageal cancer can also be performed through the exosome of saliva [55]. The expression of *GOLM1-NAA35* chimeric RNA can be used to predict the response to chemoradiation. Exosomal miRNAs derived from cancerous cells are important for metastatic procedure and drug resistance. MiR-210, abundantly detected in serum exosome and tissues from hepatocellular carcinoma patients and exosome-derived from hepatocellular carcinoma cells,

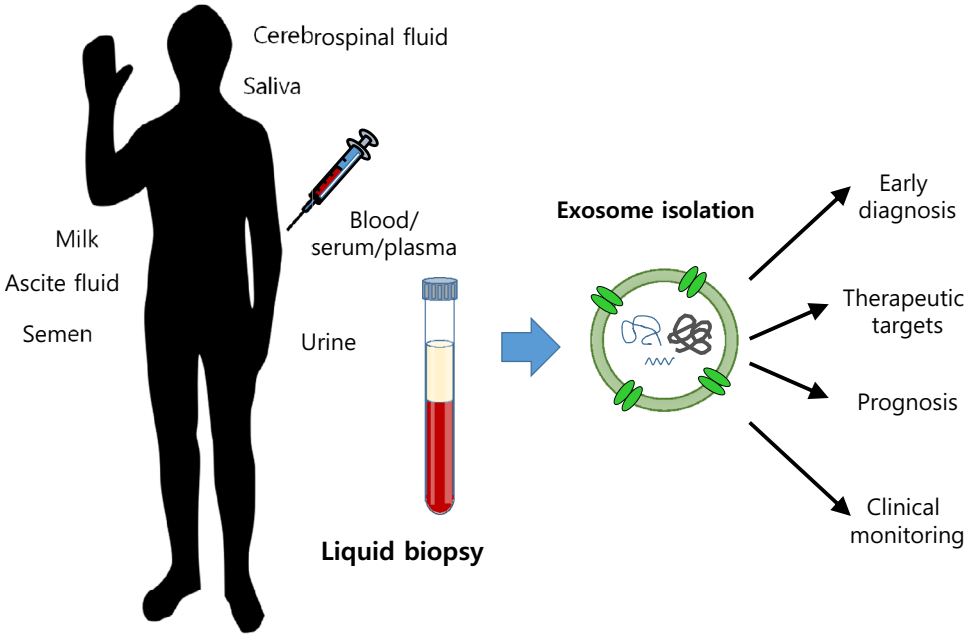

Fig. 2 Exosomes present in a number of biological fluids, including cerebrospinal fluid, milk, saliva, blood (serum/plasma) and semen can be obtained using a liquid biopsy that can be useful for early diagnosis, targeted therapy, prognosis and clinical monitoring

Table 1 Examples of cancer diagnosis using exosome

Disease target	Clinical sample	Measured biomarker	Clinical application	References
Bladder cancer	Serum	PCAT, UBC1, and SNHG16	Malignant progression	[49]
		H19		[50]
Breast cancer	Serum	miR-21 and miR-105	Metastatic progression	[51]
	Plasma	miR-155 and miR-301	Malignant progression	[52]
		miR-1246		[53]
Colorectal cancer	Serum	UCA1	Drug resistance	[54]
Esophageal carcinoma	Saliva	GOLM1-NAA35 chimeric RNA	Therapeutic response	[55]
Hepatocellular carcinoma	Serum	miR-210	Microvessel density	[56]
Lung cancer	Serum	AHSG and ECM1	Malignant progression	[58]
		miR-21-5p, miR-126-3p, and miR-140-5p		[59]
Ovarian cancer	Serum	miR-99a-5p	Malignant progression	[60]
Pancreatic cancer	Serum	*WASF2* mRNA	Malignant progression	[61]
Rectal cancer	Plasma	miR-30d-5p	Metastatic progression	[62]

is transmitted into adjacent endothelial cells leading to angiogenesis by suppressing SMAD4 and STAT6 activities [56]. Furthermore, prostate cancer derived exosomes overexpressing miR-100-5p, miR-21-5p and miR-139-5p increased the expression of receptor activator of nuclear factor kappa B ligand (RANKL) and metalloproteinases-2, -9 and -13 in cancer-associated fibroblasts that can lead to cancer progression and metastasis [57]. The expression of alpha-2-HS-glycoprotein (AHSG), extracellular matrix protein 1 (ECM1), and miR-21-5p, miR-126-3p, and miR-140-5p is higher in exosome in patients with lung cancer than in healthy group, so it could be used as a good diagnostic marker for lung cancer [58, 59]. Also, serum exosomal miR-99 is highly upregulated in ovarian cancer patients as compared to benign tumor patients or healthy women. However, the expression of miR-99 significantly decreases after surgical management of cancers. In addition, neighboring human peritoneal mesothelial cells transfected miR-99 promotes invasive properties by an increase in fibronectin and vitronetin leading to cancer growth [60]. The mRNA of a specific gene also shows clinical utility in the diagnosis of cancer through exosomes. Expression of WASF2 mRNA in exosomes isolated in serum from patients with pancreatic cancer is strongly correlated with risk of disease [61]. Highly expressed miR-30d-5p in response to hypoxia, which contributes to the

high risk of locally advanced rectal cancer, helps to predict metastatic progression using plasma exosomes in rectal cancer patients [62]. Likewise, exosomal miRNAs are important for diagnostics and therapy response in cancers.

4 Exosomes as drug delivery system for oncotherapy

The most common example of drug delivery systems (DDS) for oncotherapy include synthetic polymers, liposomes, micelles, super magnetic particles, protein and recombinant viral vectors have been developed [63–67] and some of them are currently in clinical testing [68]. A more recent addition includes smart or intelligent polymeric hydrogels that respond to external environmental changes and encapsulate or release its cargo [69]. While some of these innovative drug delivery systems have been exploited and may lead to clinical benefits in cancer patients, there are many potential barriers hinder their efficient drug delivery for their toxicity, bioavailability, stability, and target delivery. Although chemical modification, their systemic bioavailability and stability can be pursued [70–72], these strategies are associated with stronger immunogenicity against the carriers thereby leading to their quicker clearance *in vivo* [73, 74]. In this regards, the use of exosome provides an attractive alternative for targeted drug delivery.

Unlike synthetic drug delivery systems, exosomal membrane is derived from donor cell, they are non-immunogenic and thus may avoid rapid clearance from circulation and thereby increasing their bioavailability [75, 76]. Chemical drugs, proteins, RNAs, DNAs and lipids can be loaded with into exosomal cargo through different methods that can enhance their bioavailability while limiting toxicity. They are an ideal carriers for lipid-soluble drugs to the target cells. Immunogenic or toxic drugs can be encapsulated and be transmitted to target cells thereby reducing their systemic toxicity. In addition, they possess blood brain barrier passing ability [77], homing ability and cell/tissue tropism due to their surface proteins [78, 79] Exosomes can be further engineered endogenously or exogenously for the loading of therapeutic molecules (such as chemicals, nucleic acids, proteins or lipids) in order to enhance targeting efficiency and bioavailability.

4.1 Exogenous loading of therapeutic molecules to exosomes

Exosomes can be loaded with drug of interests (chemicals, DNAs, RNAs, Proteins or lipids) upon purification from producing cells or biofluids. This can be achieved by passive diffusion of hydrophobic molecules, mechanical (such as sonication), electroporation or chemical-mediated transfer (lipofection) of hydrophilic molecules by (Fig. 3). Water-insoluble chemicals (such as anti-cancer drugs) can interact and cross hydrophobic exosomal membrane under ambient conditions thereby increasing *in vivo* drug bioavailability. Indeed, exosome loaded with chemotherapeutic drugs exhibited stronger cytotoxicity against drug resistant cancer cell lines *in vitro* [80], stronger anti-tumor activity *in vivo* than that of free drugs [81].

Chemotherapeutics and large molecules, such as miRNAs and siRNAs, can also be incorporated into exosomes by electroporation [82]. Electric field creates transient pores into exosomal membrane allowing temporal movement of drugs into the exosomal lumen. Since exosomes are the natural delivery vehicles for RNAs [83, 84] which are unstable and extremely inefficient in target specificity in free form, exosomal loading of these molecules overcome these limitations. A number of studies validated successful delivery of exosome-loaded siRNAs and selective silencing of target genes [85–88]. Drug loading efficiency of chemical drugs and siRNA into the lumen of exosomes were as high as 25% for siRNA [82, 85] and 11.7% for chemical drugs [77], the accurate measurement of loading efficiency is not easy due to molecular complexity of exosomes. In addition, electroporation is known to induce vesicular aggregation [89] or siRNA aggregation [90] thereby affecting the integrity of exosome or therapeutic efficacy of RNA molecules.

In order to increase the loading efficiency and preserve the integrity of exosomes, various strategies were proposed. Pre-formed mixture of negative charged RNAs with cationic liposome can be fused with exosomes thereby incorporating RNA molecules [85, 91]. Alternatively, the hydrophobicity of siRNA or therapeutic molecules can be modified to increase its loading efficiency into exosomes. This strategy was validated in silencing of Huntington RNA by siRNA-loaded exosomes *in vitro* cultured neuronal cells as well as *in vivo* mouse striatum upon infusion [92]. Exosomal aggregation upon electroporation can be minimized by a use of trehalose pulse media (TPM) [89].

While exosomes are a natural vehicle of proteins [10], their innate chemical properties hinder their uptake into exosomes. Various strategies are developed to overcome this problem, such as simple incubation, physical insults (freeze-thawing, sonication, extrusion), permeabilization, liposome-mediate fusion and polymer-mediated transfer [93]. Haney et al. [94] reported various methods for loading exosome with catalase, 250 kDa complex and compared their loading efficiency and therapeutic efficacy *in vivo*. The study showed that permeabilization with saponin, sonication and extrusion among tested methods resulted in good loading efficiency of catalase while maintaining the exosomal integrity. Furthermore,

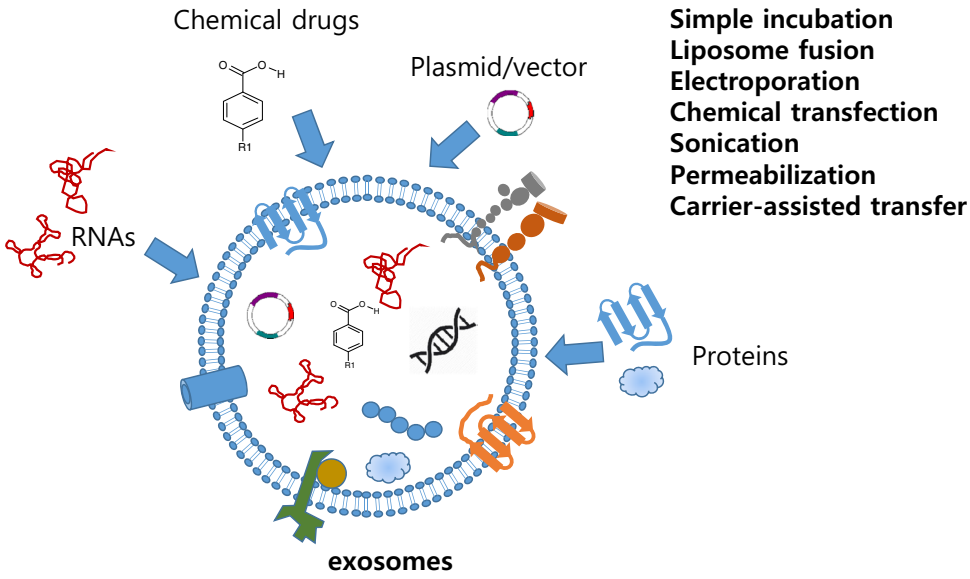

Fig. 3 Ex vivo loading of therapeutic molecules into exosomes. Exosomes can be loaded with RNAs, chemical drugs/prodrugs, plasmid/vectors, and proteins ex vivo. Therapeutic molecules can be loaded into the purified exosomes from donor cells by simple incubation, liposomes, electroporation, freeze thawing, sonication and carrier-assisted delivery

intranasal administration of catalase-loaded exosome led to behavioral recovery in murine model of Parkinson's disease demonstrating that exosome can cross the blood brain barrier for brain tumor therapy. However, mechanical or physical insults on exosomes can compromise membrane integrity as well as protein integrity [93] thereby significantly affecting their therapeutic activity.

4.2 Endogenous loading of therapeutic molecules to exosomes

Although exogenous loading of therapeutic molecules has been successfully demonstrated, clinical use requires scale production of exosome prior to *in vitro* drug packaging. In this regards, production and isolation of large quantity of exosome carrying therapeutic molecules from host cells can be an attractive alternative. Endogenous loading of therapeutic exosomes containing more therapeutic drugs (proteins and/or RNAs) can be accomplished by engineering host cells chemically or genetically. Pretreating or priming cells with chemical drugs (free or vehicle-mediated) may lead to an increase of cytoplasmic drug concentration and subsequently to their uptake into exosomal cargo.

Exosomes can be engineered to cargo chemotherapeutics at cellular level. For instance, exosomes isolated from paclitaxel-primed mesenchymal stem cells exhibited strong anti-proliferative activity to a pancreatic cancer cell line *in vitro* [95] suggesting that exosome producing cells can serve as a packaging factory chemical drugs. In another study, a synthetic fusogenic liposome-mediated transfer of chemical drugs to exosome-producing cells led to an efficient loading of the chemical drugs into exosomes [96]. Although these studies clearly demonstrated the feasibility of the endogenous drug loading to exosomes, the pitfall of these approaches is the low yield of exosomes from unmodified cells. This obstacle can be solved by one of the following 3 strategies. First, as Jang et al. [97] and Kalimuthu et al. [98] reported, mechanical extrusion of drug-primed cells generates large quantity of drug-loaded exosome-like (exosome-mimetic) nanovesicles with strong antitumor activity *in vivo*. Culturing cells in 3-dimension [99] or priming with cytokines, chemicals [100] or physical means including hypoxia [101] or hyperthermia are all known to significantly affect the yield of exosomes. Finally, exosome production from engineered cells can be enhanced by transducing some of the key genes that boost the exosome biogenesis. Indeed, Kojima et al. [102] demonstrated the feasibility of such engineered exosome for increased yield *in vitro* as well as their therapeutic usefulness in *in vivo* model of Parkinson's disease and potentially for brain tumors.

Studies have shown that exosomes isolated from host cells transfected with miRNA-encoding vectors could deliver the target miRNAs in animal models [87, 103]. For example, miR-146b-overexpressing and miR-122-overexpressing exosomes from engineered mesenchymal stem cells inhibited the glioma growth in rat brain [103] and significantly increased the chemosensitivity of hepatocellular carcinoma to sorafenib [104], respectively. Exosome loaded with anti-miR-214, siRNA to GRP78, and siRNA to PLK-1 could reduce gastric tumor growth [105] and hepatocellular carcinoma [106], respectively, by reversing their chemoresistance. Recent studies showed that RNA packaging into exosomes during biogenesis are mediated by a sets of RNA binding proteins (RBPs) and overexpression of these RBPs led to higher levels of exosomal RNAs [107, 108] suggesting that engineering of host cells

Table 2 Engineered exosomes for cancer therapy in preclinical studies

Therapeutic molecules	Exosome origin	Disease target	Drug loading	References
Chemical				
Paclitaxel	MSC	Pancreatic cancer	Endogenous, incubation	[95]
	MSC	Breast cancer	Exogenous, extrusion	[98]
	RAW264.7	Drug-resistant lung cancer	Exogenous, sonication	[80]
Doxorubicin	U937 RAW264.7	Colon cancer	Exogenous, extrusion	[97]
	DCs expressing iRGD	Breast cancer	Exogenous, electroporation	[112]
miRNA/siRNA				
Let-7a	HEK293 expressing GE11	Breast cancer with EGFR	Endogenous, transfection	[87]
miR-146b	MSC	Glioma	Endogenous, transfection	[103]
miR-122	MSC	Hepatocellular carcinoma	Endogenous, transfection	[104]
Anti-miR-214	HEK293T	Gastric cancer	Endogenous, transfection	[105]
PLK-1 siRNA	HEK293 + MSC	Bladder cancer	Exogenous, electroporation	[88]
GRP78 siRNA	MSC	Hepatocellular carcinoma	Endogenous, lipofection	[106]
Proteins/mRNA				
TRIM3	Gastric cancer cells	Gastric cancer	Endogenous, transfection	[109]
CD-UPRT fusion protein	HEK293T	Schwannoma	Endogenous, transfection	[111]
TRAIL	K562	Lymphoma	Endogenous, transduction	[110]

with these RNA and/or protein sorting machineries may provide efficient tools for the packaging of theses therapeutic molecules into exosomes and for their clinical applications. Thus, the delineation and exploitation of exosomal sorting machineries as well as ligand-receptor web of exosomal proteins will open new avenues for targeted drug delivery.

While exosomes contain proteins and RNA cargo *in vivo* and are difficult to incorporate these large molecules *in vitro*, the genetic modification of exosome-producing cells is one of the most preferred strategy for active packaging of therapeutic RNAs or proteins. Exosomal delivery of TRIM3, a potential tumor suppressor for gastric cancer cell proliferation and migration, inhibited gastric cancer progression and metastasis [109]. Exosomes from TRAIL- or suicide gene-transduced exosome producing cells induced a significant tumor inhibition in animal tumor models [110, 111]. Studies also demonstrated that exosomes from genetically modified host cells with transgenes encoding model proteins, including ovalbumin, catalase and glial cell-line derived neurotropic factor, successfully delivered the proteins to target tissues and exhibit therapeutic efficacy in the animal model of Parkinson's disease. Utilizing of targeting ligands on the engineered exosome can further enhance the targeting efficiency [112]. Ohno et al. [87] demonstrated that targeted delivery of miRNA-loaded exosomes could be greatly enhanced by EGFR ligand expression on the surface of exosomes in a mouse model. The finding of Grapp et al. [113] that folate receptor-α on exosomal surface plays an important role in the blood–brain barrier (BBB) crossing and delivery of therapeutics into brain parenchyma suggesting that engineering host cells with this exosomal membrane protein can be used in cerebral drug targeting for the treatment of neurodegenerative disease or malignancy. Engineering exosomes to carry ligands for adhesion molecules or surface receptors on the exosomal membrane can facilitate the targeted delivery of their cargo to cells with corresponding receptors [96, 111–113]. These studies highlighted the therapeutic potential of engineered exosomes as DDS for the treatment of cancer. Translational applications of engineered exosomes for cancer therapy are summarized in Table 2.

5 Conclusions

Exosomes clearly play key roles in cancer development. Exosomal biomarkers can greatly improve theragnostics of cancer patients by liquid biopsy. In addition, the use of engineered exosomes may represent a new class of drug delivery system for their ability to cross biological barriers with little or no safety concerns associated with therapeutics, including drug toxicity, immune responses, biodistribution and targeted delivery. Low stability and/or transducibility of therapeutics (chemical drugs, proteins, and RNAs) in circulation can be solved by encapsulating them into exosomes. To increase the therapeutic efficacy of exosomes, a number of endogenous or exogenous loading strategies have been developed and validated *in vitro* as

well as *in vivo* animal models. Promising results of this cell-free therapeutics were obtained from a number of relevant animal models for human diseases and clinical translation of exosomes has already initiated in cancer therapy and organ transplantation and their safety was validated. Although further studies are required to standardize methods involved in exosome purification and characterization for their application as a drug delivery system in clinical research, the engineered exosomes may serve as an ideal DDS for cancer therapy due to their high biocompatibility, minimal toxicity, low immunogenicity with high target specificity in future. However, successful clinical translation of exosome-based therapeutics critically depends on not only our understanding of the therapeutic mechanisms of exosomes, but also our ability to isolate as well as design exosomes for their optimal potency to cure or treat diseases.

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Author contributions WL: manuscript writing, conception and design, HSK: manuscript writing and final approval of manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical statement Ethical approval and consent to participate is not applicable to this article as no data were generated or analyzed during the current study.

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