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REVIEW

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Therapeutic combinations of exosomes alongside cancer stem cells (CSCs) and of CSC-derived exosomes (CSCEXs) in cancer therapy

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Abstract

Exosomes which are membrane vesicles released by cells have gained significant interest in the field of cancer therapy as a novel means of intercellular communication. Their role in immune activation and their pathophysiological functions in cancer therapy have been recognized. Exosomes carry diverse bioactive components including proteins, mRNA, microRNAs, and bioactive lipids. These molecules have therapeutic potential in promoting tissue regeneration, supporting stem cell activity, preventing cell death, modulating immune responses, and promoting the growth of new blood vessels. However, the precise roles of exosomes derived from mesenchymal stem cells (MSCs) in the treatment of various cancers are still not fully understood. Consequently, cancer stem cells (CSCs) can self-renew and differentiate into various cell types. Understanding the mechanisms that sustain their persistence is crucial for developing effective therapies. Exosomes have recently gained interest as vehicles for intercellular communication between CSCs and non-CSCs, influencing cancer progression and the microenvironment. Research is ongoing on the utilization of exosomes derived from cancer stem cells (CSC-Exosome) for cancer treatment. The composition of extracellular vesicles is influenced by the specific type and condition of the cells from which they are secreted. Circulating exosomes contain stable RNA molecules such as mRNAs, microRNAs, and long non-coding RNAs (lncRNAs). In this review, we will explore the significance of exosomes and their diverse cellular combinations in the context of cancer therapy.

Keywords Exosomes, Cancer stem cells, Cancer therapy, Cellular combinations

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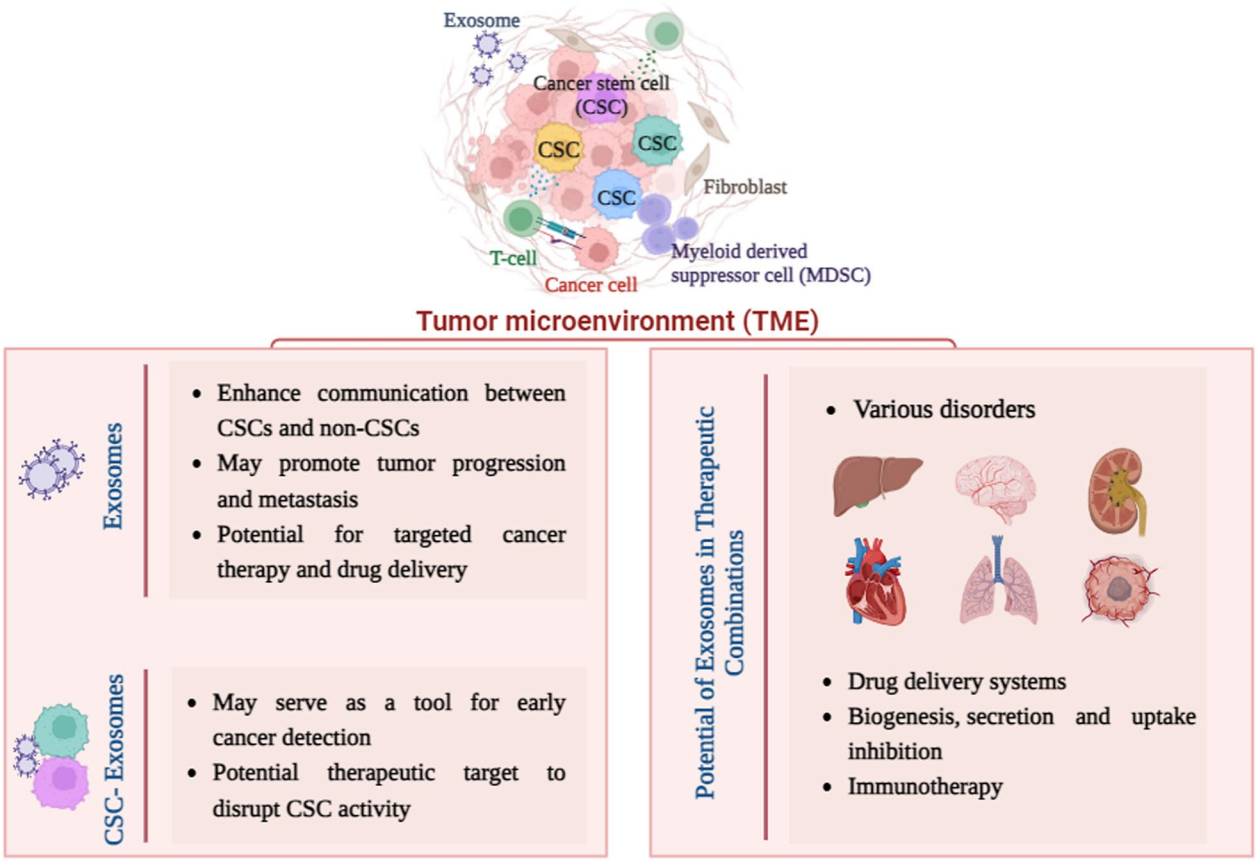
Graphical Abstract



Introduction

Exosomes are small biovesicles that originate from the endosomal pathway and are released into bodily fluids when multivesicular bodies fuse with the plasma membrane. They contain cell-specific cargoes, including proteins, lipids, and genetic materials. These cargoes can be absorbed by nearby or distant cells to affect their biological activities. This unique capability positions exosomes as highly promising candidates for use as non-invasive diagnostic biomarkers and therapeutic delivery vehicles [1, 2]. Early studies showed that exosomes originate from inside cells. These studies examined how exosomes help remove proteins from the surface of developing blood cells as they transform into red blood cells [3]. Since exosomes were first discovered in reticulocytes, a type of blood cell, it has been found that many types of cells, especially different kinds of cancer cells, release exosomes into the extracellular space. Exosomes can be commonly found in body fluids such as blood, saliva, and urine [4]. Despite ongoing research, the full significance of exosomes in biology is not yet fully understood. Exosomes are believed to facilitate cell communication by sharing active substances, which can impact the function of target cells and play a role in various bodily functions and diseases [5]. These membrane systems allow large molecules, such as proteins, fats, and DNA, to be transported from one cell to another over long distances without being harmed [6]. The study of exosomes has made significant progress since the 1970s [7, 8]. Pan et al. coined the term "exosome" to describe these particles, which were subsequently characterized as being derived from the endocytic pathway and released by various cell types. In addition, Zitvogel et al. demonstrated that exosomes play a role in antigen presentation to immune cells, suggesting their involvement in intercellular communication [7, 9, 10]. The field gained momentum in the 1990s by discovering exosome involvement in intercellular communication and their potential as therapeutic agents [11]. In the 2000s, isolation techniques and the identification of microRNAs within exosomes.

In recent years, exosome engineering and clinical trials have become prominent in research [9, 12, 13]. Current exosome research focuses on developing targeted therapies, integrating exosomes with other technologies, and addressing ethical considerations [14, 15] (Fig. 1).

Source and structure of exosomes inside cells

Exosomes which are approximately 30–100 nm wide [16] are formed through a process called endocytosis. During this process, a paortion of the late endosome membrane folds in, leading to the creation of multivesicular bodies (MVBs) containing small vesicles filled with fluid from the cell (ILVs). The MVB can either merge with the outer cell membrane to release the ILVs as exosomes into the extracellular space or fuse with lysosomes to degrade the contents [2]. The number, generation, and eventual location of ILVs and exosomes are regulated by various cellular processes. These processes collaborate meticulously and are closely managed during the movement of membranes involved in endocytosis [17]. This guid aims to assist researchers in selecting the most appropriate isolation methods for exosomes based on their research objectives and available resources.The creation and release of exosomes are important for making related proteins and sorting their contents [18]. The creation and release of exosomes are also managed by other methods that do not depend on ESCRT [19]. Exosomes are different from other small particles that come from cells because of their source, size, appearance, and composition. Often researchers, identify the type of vesicle by looking at it under an electron microscope and checking for certain specific proteins [20]. All exosomes have specific proteins because they come from endosomes. These include proteins that help move things in and out of cells, like Rab GTPases and Annexins. They also have heat-shock proteins and other proteins that help form multivesicular bodies (MVBs), as well as tetraspanins such as CD9, CD63, CD81, and CD82 [21, 22]. Based on their origin and intended function, exosomes may exhibit unique proteins specific to certain cell types. For example, mature dendritic cell exosomes have a lot of MHC class II and CD86, which aid in the activation of CD4 + T cells. Studies of lipid content have revealed that exosomes contain significant amounts of cholesterol from lipid rafts, along with a type of fatty substance called ceramide and other types of fats [23]. Besides proteins and fats, exosomes can also carry nucleic acids, especially mRNA and microRNA. These can influence how recipient cells express proteins and signal each other [24]. Table 1 shows a summary of different standard methods used to separate exosomes. Exosomes are made by cells that carry different types of molecules. The table shows a summary of different ways used to collect exosomes from biological samples. These techniques include spinning things fast (ultracentrifugation), separating based on how heavy something is (density gradient centrifugation), sorting based on size (size exclusion chromatography), using antibodies to find specific things (immunoaffinity methods), and making things clump together (precipitation methods). Each method is explained, including what is good about it, what it's not so good at, and what kinds of samples it works best with.

Roles of exosomes in intercellular communication

Exosomes can be thought of as small versions of the cells they originate from. They contain a like fluid and have the same orientation as the outer membrane of the cell. This means that the external part of the cell membrane faces outward, displaying specific proteins and receptors that can be used to measure interactions with other cells

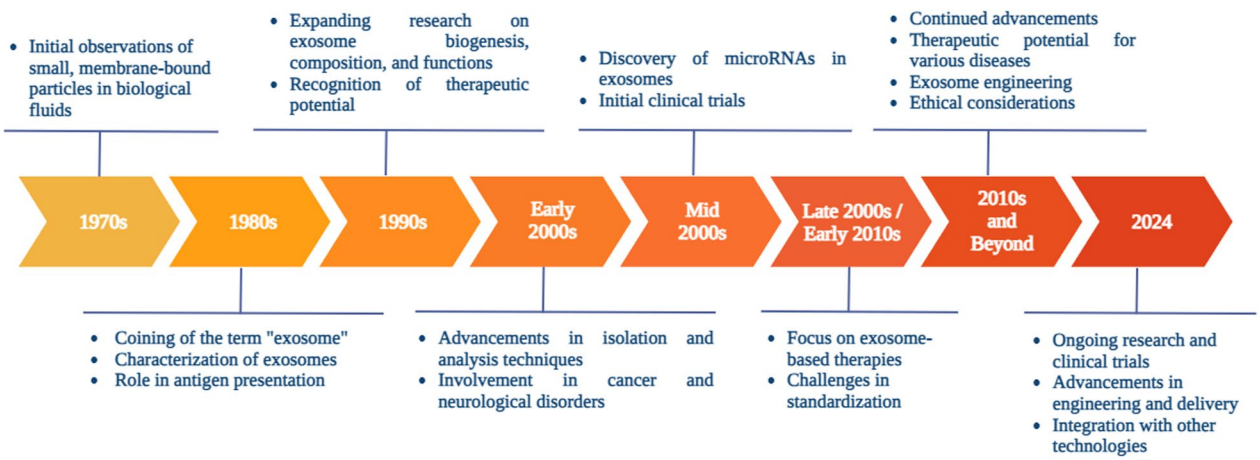


Fig. 1 A decade of exosome research: from discovery to cutting-edge applications

Table 1 Different standard methods for separating exosomes

Techniques	Advantage	Disadvantage	Time
Ultracentrifugation (UC)	• Bulk purification • Isolation of total EVs • Vesicle structure maintained • Low reagent cost	• Time-consuming • The isolation efficiency is rather low • Low isolation efficiency • Unable to differentiate exosome and other contaminants like microvesicles and proteins	5–10 h
Tangential Flow Filtration (TFF)	• Large scale volumes • Efficiency • Flexibility • Self-cleans	• Unable to differentiate exosome and other contaminants like EV, nucleic acid, and proteins	Less than 2.5 h
Size Exclusion Chromatography (SEC)	• Resolve vesicles of different sizes • Gentle, non-adsorptive interaction with the sample	• Contaminations Pressure caused damage	2–4
Polymer Precipitation (PP)	• Less time intensive • Fewer steps than in the UC • uses water-excluding polymers	• Unable to differentiate exosome and other contaminants like EV, nucleic acid, and proteins • Low purity • Moderate yield • Require pre-/post-treatment cleanup	30 min–12 h
Density gradient	• High purity • Vesicles divided into various populations	• Loss of exosomes • Skillful technique • Time-consuming • Labor-intensive • Low yield	14–18 h
Immunoaffinity	• Exosome enrichment established on standard markers • High purity • Molecular selection of exosome • Moderate to low sample volume • Compatibility for high-throughput sample preparation	• High cost • Antibody cross-reactivity • Alterations in markers on exosomes • Heterogeneity in surface marker expression restricts isolation purity	2–6 h

[25]. Exosomes are small particles that are released from cells and play an important role in the extracellular environment. They are then dispersed to various locations where they interact with recipient cells [26]. The mechanisms by which exosomes connect with recipient cells have been explained through several methods. Exosomes can merge with the outer layer of the target cell, merging their contents with the target cell's membrane. Alternatively, exosomes can activate cell surface receptors by using special lipids and proteins and showing antigens to these receptors [2, 27]. Also, recipient cells might take in exosomes through methods like pinocytosis, phagocytosis, or receptor-mediated endocytosis [28]. It was later discovered that exosomes are integral for displaying antigens and facilitating communication between cells. They serve as crucial carriers in immune responses. [29]. Consequently, novel applications for exosomes are being proposed as researchers study how different cells and tissues produce them. Exosomes might help with blood clotting, moving cells, growing new blood vessels, healing wounds, fighting inflammation, and controlling how cells behave [30–32]. Hematopoietic cells, gut cells, fat cells, nerve cells, connective tissue cells, and some cancer cells have all been shown to send out exosomes into fluid outside their cells in lab studies. Many body fluids, like blood, joint fluid, urine, saliva, milk, and fluids from the chest and abdomen, contain a substantial amount of exosomes [33, 34].

The dual role of exosomes in tumor biology

Exosomes, secreted by various cell types, play a pivotal role in tumor biology. These nanovesicles serve as crucial mediators of intercellular communication, facilitating the transfer of molecular signals that can influence cancer progression, metastasis, and immune evasion [27].

Exosomes derived from cancer cells can promote tumor growth and progression through various mechanisms. They can transfer oncogenic factors, such as microRNAs and proteins, that enhance the malignant characteristics of tumor cells. For instance, exosomes can stimulate angiogenesis, facilitating nutrient supply to tumors [35]. Moreover, exosomes can modify the behavior of nearby cells, creating a supportive niche for tumor growth and metastasis [36].

Furthermore, exosomes play a crucial role in metastasis, enabling cancer cells to invade distant organs. They can prepare pre-metastatic niches by altering the extracellular matrix and modulating the immune response.

This strategic manipulation of the microenvironment allows for more effective colonization of metastatic sites [37].

Following this, tumor-derived exosomes can suppress anti-tumor immunity by carrying immunosuppressive molecules that inhibit T-cell activation and promote regulatory T-cell expansion. Indeed, this dual role of exosomes in suppressing immune responses while simultaneously promoting tumor growth emphasizes their importance in oncological contexts [38].

Despite their supportive roles in tumor biology, exosomes also offer therapeutic potential. Engineered exosomes can be used for targeted drug delivery or as vehicles for RNA-based therapies. This highlights the need to distinguish between the pro-tumorigenic and anti-tumorigenic roles of exosomes, providing a balanced view of their significance in cancer research [39].

Conclusively, exosomes are powerful modulators of tumor biology, influencing cancer progression, metastasis, and immune evasion. Their dual roles present both challenges and opportunities in the oncological landscape, making them a critical focus for future research and therapeutic strategies [40].

Exosomes from cancer stem cells (CSC-exosomes)

Extracellular vesicles (EVs) can be classified into three types based on their formation and release: exosomes, microvesicles, and apoptotic bodies [41]. EVs produced by CSCs serve multiple functions, including displaying distinct signals on their surface and transporting materials to other cells in the tumor area. It is believed that exosomes released by cancer stem cells (CSCs) contribute to the formation of the pre-metastatic niche. These exosomes increase the ability of CSCs and similar cells to spread cancer to other parts of the body [42, 43].

The cargo of CSC-exosome and their effects

Researchers have identified a type of RNA called H19, which is produced by cancer stem cells (CSCs) and is carried out of the cell in small vesicles known as exosomes. These exosomes are then absorbed by nearby cells, allowing them to take in specific small molecules called miRs, particularly let-7 [44]. Exosomes from breast cancer stem cells have a lot of certain molecules called miRs that are connected to cancer spreading. Another study discovered that exosomes from cancer stem cells made cancer cells more resistant to chemotherapy drugs like doxorubicin and paclitaxel by using miR-155. The resistance to breast cancer therapy is driven by the induction of epithelial-to-mesenchymal transition (EMT) and involves the activation of anti-apoptotic pathways and drug efflux pumps. MiR-155 plays a significant role in EMT and resistance. Exosomes released by cancer stem cells and resistant breast cancer cells carry miR-155, which can be delivered to sensitive cells, resulting in the development of a resistant phenotype. Similar findings were observed in epithelial ovarian cancer cells and gastric cancer cell lines, where exosomes facilitated the transfer of chemoresistance traits through the delivery of miR-155 and the induction of EMT [45, 46]. Exosomes containing miR-30a and miR-222 were found to enhance the aggressiveness of cancer cells in colon cancer stem cells [47]. In the study on CSC-Exosomes from stomach cancer, 11 unique miRNAs were identified. These miRNAs could potentially aid in the diagnosis of metastasis, which occures when cancer spreads to other parts of the body. CSC-Exosomes from gliomas were found to contain high levels of miRNA-21, which in turn increased the production of vascular endothelial growth factor (VEGF) and promoted blood vessel growth [48]. Further analysis showed that Linc01060 was found in cancer stem cells of glioma with low oxygen levels. This molecule triggered processes that promote cancer growth in glioma cells, leading to more serious disease [49]. Additionally, lung cancer stem cell exosomes were found to increase the likelihood of metastasis by upregulating a molecule called miR-210-3p, which affects the FGFRL1 receptor [50]. Researchers found that exosomes derived from stem cells of oral squamous cell carcinoma exhibited elevated levels of miR-21 and reduced levels of miR-34, which contributed to cancer growth. In a separate study, exosomes from gemcitabine-resistant pancreatic cancer stem cells were shown to contain higher amounts of miR-210. This microRNA was transferred to other cancer cells, conferring resistance to the drug. To assess the efficacy of exosomes in drug delivery, several studies have employed techniques such as flow cytometry, confocal microscopy, and quantitative real-time PCR to track the uptake of exosomes by target cells and measure the delivery of encapsulated molecules. For example, used flow cytometry to quantify exosome uptake by tumor cells and analyzed the expression of encapsulated miRNAs using quantitative real-time [51–53]. Exosomes derived from cancer stem cells (CSCs) and non-cancer stem cells in prostate cancer contain distinct types of miRNA. Specifically, CSC-derived exosomes are involved in preparing the surrounding environment for future cancer metastasis [54]. For instance, miRNA-19b-3p promotes the growth of new blood vessels, helping the formation of areas where cancer can spread. It also contributes to cancer dissemination and a process known as EMT when present in CSC exosomes in kidney cancer [55]. Additionally, the transfer of lncRNA facilitated the EMT process in papillary thyroid cancers [56]. Table 2 gives a summary of the miRNAs found in exosomes from various types of cancer. These exosomes contain a diverse range of miRNAs

Table 2 Exosomal miRNAs in cancers

Cancer	Exosomal miRNA	Function in cancer	Refs
Gastric cancer	miR-106a-5p	Contributed to the promotion of 5-fluorouracil resistance	[57]
	miR-421		[58]
Colorectal cancer	miR-214	Increases cell's resistance to mitomycin	[59]
	TUBB3	Promotes metastasis and proliferation	[60]
	miR-143	Promotes cell proliferation and migration	[61]
	miR-141	Promotes the stemness and chemoresistance	[62]
	HUR	Suppresses cell apoptosis and promotes chemoresistance	[63]
	miR-221	Promotes cell proliferation	
	miR-1273 g-3p	Promotes cell viability	[64]
	miR-128-3p	Involved in the transmission of an oxaliplatin-resistant phenotype to colorectal cancer cells with a sensitivity	[65]
	miR-31-5p		[66]
	RORγt	Promotes Th17 cell differentiation	[67]
	miR-342-3p	Promotes proliferation, invasion, and migration	[68]
	miR-17-92a	Early-stage tumorigenesis	[69]
	miR-590-3p	Tumor proliferation and metastasis	[70]
	miR-26a	Invasion and metastasis	[71]
	miR-26b		
Breast cancer	miR-1246	Increasing the sensitivity of cells to cisplatin, docetaxel, epirubicin, and gemcitabine	[46]
	miR-423-5p		
	mir-19a	Promote cancer cell proliferation and tumor invasion	[72]
Ovarian cancer	miR-1246	Involved in giving nearby cancer cells paclitaxel resistance	[73]
Glioblastoma	miR-1238	involved in the transmission of temozolomide resistance to susceptible glioblastoma cells	[74]
	miR-151a		[75]
Pancreatic cancer	miR-155	Increased ROS elimination and resistance to gemcitabine	[76]
	miR-210		
Esophageal cancer	miR-26a	Migration and metastasis	[77]
Lung cancer	miR-100-5p	Involved in cisplatin-resistant lung cancer cells to sensitive lung cancer cells transfer	[78]
	miR-29c-5p	Sensitive cells were given doxorubicin-resistant phenotypes	[79]
	miR-29b-2-5p		
	miR-139-5p		[80]
	miR-204-5p		[81]
	miR-204-3p		
	miR-551b-3p		[82]
Non-small cell lung cancer	miR-425-3p	Induced resistance to cisplatin and gefitinib in nearby cells, respectively	[83]
	miR-214		[84]
Tumor-associated macrophages	miR-365	Playing a role in pancreatic cancer cells' increased gemcitabine resistance	[85]
	miR-21	Causing gastric cancer cells to exhibit increased cisplatin resistance and decreased cell apoptosis	[86]
	miR-223	Involved in ovarian cancer cells' induction of the cisplatin-resistant phenotype	[87]
Cancer-associated fibroblast	miR-16	Enhanced breast cancer cell metastasis and migration	[88]
	miR-148a		
	miR-21	Involved in the transmission of paclitaxel resistance to ovarian cancer cells	[89]
	miR-196a	Involved in giving head and neck cancer cells cisplatin resistance	[90]
	miR-106b	Involved in enhanced gemcitabine resistance and pancreatic cancer cell proliferation	[91]
	miR-146a		[92]

that play crucial roles in cancer growth and metastasis. The table presents a comprehensive list of these exosomal miRNAs, arranged by cancer type, offering valuable insights for their potential use in diagnostic tests or as therapeutic targets. This summary underscores the significance of exosomal miRNAs in cancer research and

their potential applications in future studies and medical interventions.

In this explanation, Fig. 2 shows how cargo is moved by exosomes. The sorting and mixing of cell materials into MVBs are helped by the ESCRT system. The careful addition of parts from secretory cells creates MVBs. These MVBs can join with lysosomes to break down materials or connect with the cell's outer membrane, releasing exosomes into the space outside the cell through a process called exocytosis. Exosomes hold different types of materials, including mRNAs, lncRNAs, miRNAs, proteins, and transcription factors. When exosomes reach their target cells, they can either combine with the cell's outer layer or be taken in by the cell. Using these methods, the proteins and RNA in exosomes can be sent into the liquid inside the cells or become part of the cell membranes. Also, exosomes can talk to target cells using special proteins on their surface, allowing them to connect directly with other cells [29, 93–95].

Distinguishing characteristics of CSC-exosome

Even though cancer stem cells (CSCs) are difficult to locate within a tumor, scientists are currently investigating the collaborative function of CSC exosomes and tumor exosomes (TEXs). Unlike exosomes made from regular tumor cells, the exosomes from cancer stem cells in human prostate cancer have their unique miRNA, like a high level of has-miR-1307-5p [54]. Exosomes released by normal cells and stem-like cells in stomach cancer exhibit distinct patterns of miRNA expression [48]. The markers present in CSCs contribute more to the spread of cancer compared to those found in regular tumor cells. Both CSC-exosomes and tumor exosomes (TEXs) can help tumors grow [96]. In order to confer resistance to cell death, enhance mobility, and alter the properties of non-cancer stem cells, pancreatic cancer stem cell exosomes deliver the CD44v6 marker to these non-cancer stem cells. It's interesting to see that mice that received injections of colorectal CSC-Exosomes exhibited prolonged presence of neutrophils in their bone marrow, which displayed increased indications of cancer development. More research is needed to clearly explain the differences in markers and biological activities between CSC-Exosomes and non-stem TEXs [97, 98].

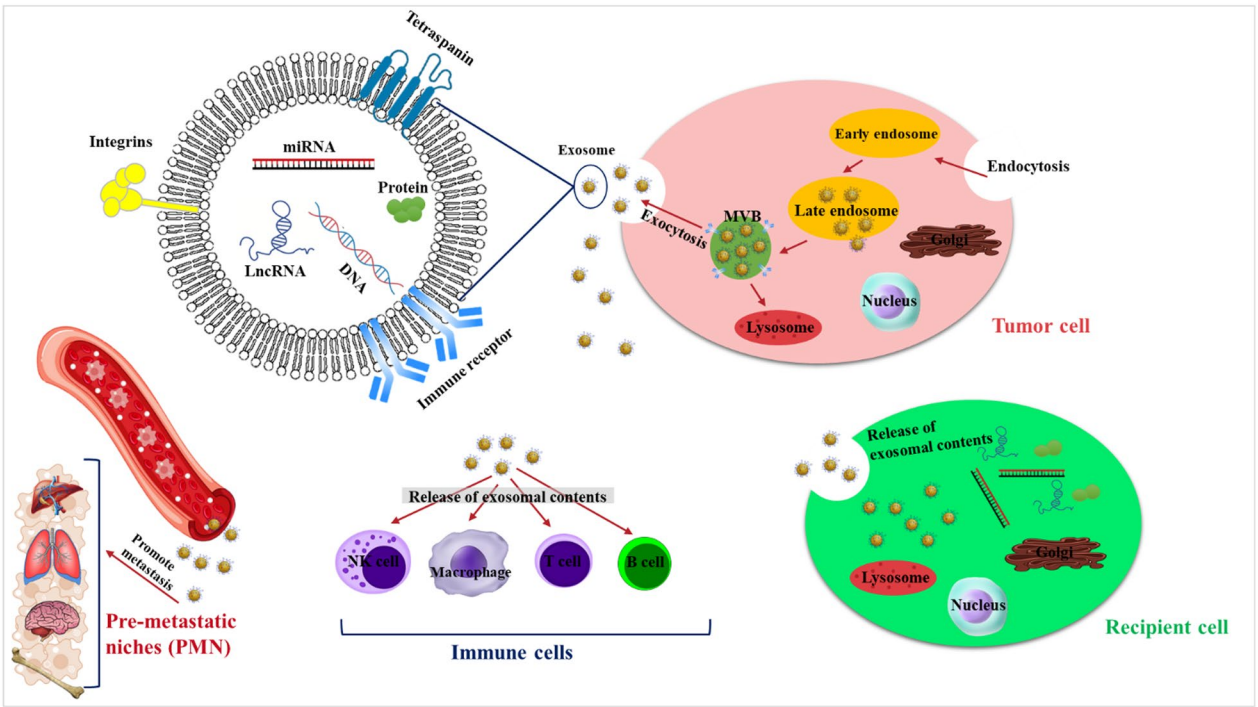


Fig. 2 Moving materials using exosomes. ESCRT sorts and adds content into MVBs. The careful addition of parts from secretory cells leads to the creation of MVBs (multivesicular bodies). MVBs can either combine with lysosomes to break down their contents or merge with the cell's outer layer to release exosomes outside the cell. Exosomes transport RNA molecules (like mRNAs, lncRNAs, and miRNAs), proteins, and other important factors that help in gene activity. Exosomes can either fuse directly with the surface of the target cells or they can be taken in by the cells. Proteins and RNA are sent into the cytosol or the outer layer of other cells through both methods. Exosomes can talk to specific cells directly using special proteins on their surface

The role of CSC-exosomes in cancer environment and growth

The process by which cancer stem cells change into cancer cells and subsequently revert to cancer stem cells is complicated. Exosomes are important for managing the balance between cancer stem cells and regular cancer cells because they help with communication between all the cells in the tumor area. CSCs help cancer grow by releasing signals that keep cancer cells behaving like stem cells. So far, people have mostly assumed that exosomes from cancer stem cells will show this trait and help create an environment that can lead to tumors [52]. Many features of exosomes derived from cancer cells (CDEXs) are similar to the new roles found for exosomes originating from cancer stem cells (CSC-Exosomes). It is important to note that distinguishing between exosomes made by cancer stem cells and similar types found within complex tumor tissues proves to be challenging based on numerous studies. The functions of CSC-Exosomes, which have recently been discovered in a few studies, are explained above about known markers and the cargo they carry [99].

CSC-exosomes and how they affect cancer stem cells

The interaction between cancer stem cells (CSCs) and regular cancer cells, is facilitated by exosomes, which act as carriers of important signals for managing the development of CSCs and the changes in regular tumor cells, helping keep the balance in the cancer environment. In breast cancer, certain cancer cells exhibit stem cell-like behavior and produce exosomes that carry mRNA messages linked to cancer spread and stem cell function. These exosomes promote the growth of tumors in other cells. The Wnt signaling pathway, which is essential for growth, development, metabolism, and the maintenance of healthy stem cells, is also involved in cancer progression. However, when this pathway becomes activated inappropriately, it can lead to tumor formation and impact the renewal and development of cancer stem cells. There is compelling evidence demonstrating fibroblast exosomes induce colorectal cancer cells to exhibit stem cell characteristics, such as the ability to form spheres and grow tumors. They also increase the number of cancer stem cells in colorectal cancers by activating the Wnt signaling pathway. Additionally, exosomes derived from mesenchymal stem cells (MSCs) activate the Wnt signaling pathway, promoting the growth of breast cancer cells. Exosomes from surrounding cells in lymphoma help change side-population cells into non-side-population cells by carrying the Wnt signaling pathway in cells activated by Wnt3a [100, 101].

EMT and CSCs

The formation of pre-metastatic niches and the recruitment of bone marrow cells occur when other cells take in tissue-specific exosomes (TEXs). This process is influenced by the ability of cancer stem cells (CSCs) to self-renew and differentiate into different cell types, which is strongly influenced by a process called EMT [102]. Through EMT, these cells can gain traits similar to stem cells. Transforming growth factor beta (TGF)-β can start a process called EMT. Exosomes from chronic myeloid leukemia carry a substance called TGF-β1 to other cells. This helps the leukemic cells grow and can lead to the formation of tumors. Claudin 7 is sent into less aggressive cancer cells by exosomes made by the cells that start colon cancer. This process helps change these cells [103]. Reports suggest that CSC-Exosomes carry miRs and lncRNAs that control how CSCs release substances and resist treatment [104].

CSC-exosome and the delivery of reprogramming factors

Exosomes help keep cancer stem cells stable by carrying important proteins or by managing how much of these proteins are made in other cells [105]. Abnormal changes in certain proteins that control gene activity in tumor tissues can lead to normal cancer cells becoming cancer stem cells. Exosomes contain miRNAs that play a vital role in regulating tumor cell growth, survival, and tumor formation. For instance, gastric cancer cells release exosomes containing let-7 microRNAs into the tumor microenvironment, promoting cancer aggressiveness and faster growth. Melanoma cells produce a molecule called miR-222 in exosomes, which can make the cancer aggressiveness. Additionally, tumor cell-derived exosomes are rich in miR-21 and miR-34a molecules miR-21 and miR-34a [106].

Effects of CSC-exosome on the immune system in tumor microenvironment

Recent research shows that CDEXs or TEXs help suppress the immune system in tumors [107]. However, we need to exercise caution before assuming that CSC-Exosomes behave similarly in altering the tumor microenvironment [108]. Exosomes released by brain tumor stem cells contain Tenascin-C, which lowers the activity and growth of T cells. Colorectal cancer stem cells release tiny particles that elevate interleukin-1 levels, leading to the support of tumor growth by neutrophils [109]. In another study, exosomes from colorectal cancer stem cells were introduced to dendritic cells (DCs) causing T-cells to specifically target cancer stem cells. Exosomes from glioblastoma stem cells utilize the STAT-3 pathway to convert monocytes from the M1 type to the M2 type, creating an immune-suppressing environment [110].

CSC-Exosomes also impact the presence of programmed cell death ligand 1 (PD-L1) in macrophages and the transformation of monocytes into myeloid-derived suppressor cells. Additionally, cancer stem cells in glioblastoma produce macrophage migration inhibitory factor (MIF), which encourages the development of myeloid-derived suppressor cells (MDSCs), and further weakens the immune system [111]. In a kidney cancer model, CSC-derived extracellular vesicles (EVs) hindered the development of DCs and immune responses from T cells [112]. The interaction between cancer stem cells (CSCs) and exosomes holds promise for developing new cancer treatments that focus on the immune system; however, many questions remain regarding how CSC-Exosomes precisely influence the immune system in tumors [113, 114]. Importantly, the association and impact of CAR T-cells with exosomes must be investigated and also the significance e of hub long non-coding RNAs along with lncRNA-miRNA-mRNA are of great importance [115, 116].

MSC-derived exosomes may help in healing and repairing the body

The field of regenerative medicine sees the healing potential of exosomes that come from human mesenchymal stem cells (MSCs). MSCs are special cells that can help keep tissues healthy. They can migrate to injured areas and impact various bodily processes, such as immune system regulation, energy provision, and tissue repair [117]. These processes happen because cells interact directly with each other or through nearby signals. This involves the release of exosomes that carry biological information [118]. Notably, exosomes and other small particles released by MSCs are important for keeping the tissue environment healthy and promoting healing. Exosomes contain beneficial substances like proteins and RNAs, enhancing their chemical functionality [119]. Exosomes elicit a reduced immune response than whole stem cells. They do not differentiate into adult cells or create tumors. Because of these qualities, there is significant interest in using them as a way to deliver treatments that help repair tissues without using actual cells [120]. Research shows that exosomes made by MSCs from different sources have different characteristics and contain a wide range of functional parts [121]. Exosomes from MSCs found in umbilical cords, fat tissue, and bone marrow have different types of proteins and could be helpful for treatment. Also, when looking at stem cells from different sources, exosomes from adipose tissue (AT-MSC) show the highest level of activity in sending out signals and controlling immune responses. In contrast, exosomes from umbilical cord stem cells (UCMSC) mainly help with healing tissues [122]. BM-MSC exosomes can greatly help in healing by promoting growth. While the precise mechanisms through which exosomes from MSCs aid in tissue repair remain unclear, numerous studies suggest they operate through diverse pathways. For example, they support the maintenance of existing stem cells by promoting their proliferation and self-repair. Additionally, they could facilitate healing by helping cells multiply, support the growth of new blood vessels, and assist in repairing damaged tissues. Improving tissue damage and stopping cell death using different methods; lowering oxidative stress and managing the immune response by sending special substances to injured tissue [123–125]. Exosomes, which are tiny particles made by MSCs, can help fix tissue damage. They do this by carrying important molecules that influence other cells. This process helps change how damaged cells behave and how they express their genes [126, 127]. Exosomes from MSCs seem to help treat and diagnose different health problems, like brain disorders, liver, kidney, and lung damage, and heart diseases [124].

Cardiovascular disorder

The leading cause of death worldwide is cardiovascular disease (CVD) [128]. Insufficient formation and multiplication of local heart cells weaken, and the heart's ability to heal and regenerate [129]. Recent studies have shown that exosomes from MSCs help protect the heart during heart injuries. Exosomes from heart stem cells might help damaged heart tissue release signals that promote the growth of new blood vessels, like stromal cell-derived factor (SDF) and VEGF. Some miRNA molecules, like miR-221 and miR-19a, might be better at preventing CMC and helping with healing from blood flow damage. These molecules are found in exosomes produced by GATA-4 gene-modified stem cells. By inhibiting the production of the cell death-triggering protein called PUMA, miR-221 may enhance the survival of heart muscle cells during periods of reduced blood flow. Additionally, miR-19a may facilitate the growth and survival of cardiac myocytes by activating important cellular survival signals and reducing levels of PTEN, a controlling factor in these signals [130, 131]. Also, MSC exosomes contain a lot of miR-210, which might help new blood vessels grow and make the heart work better in animal models of heart attacks. They do this by reducing the amount of a protein called ephrin-A3 in the cells that line blood vessels, and this protein normally stops new blood vessels from forming [131]. Another study showed that MSC exosomes had a positive effect on heart cells. They help the cells to stay healthy and live longer by reducing damage from stress, boosting energy production (like ATP and NADH), and activating pathways that prevent cell death by modifying certain proteins (Akt and GSK3). The study also found

that MSC exosomes lowered the activity of certain pathways that lead to cell death by decreasing the levels of c-Jun NH (c-JNK). In a study using mice with heart problems, MSC exosomes helped to improve heart function and reduce the size of heart damage [132]. Additionally, research has shown that cardiac MSC-EVs help support the growth of new blood vessels and make human umbilical vein endothelial cells (HUVECs) grow faster, form better structures, and live longer. The Angiopoietin-1 (Ang1)/Tie-2 signaling pathway was mainly activated by the actions of human cardiac MSC-EVs that promote the growth of new blood vessels [133]. Other studies showed that exposure to PDGF increased the ability of EVs from AT-MSCs to stimulate blood vessel growth. PDGF-treated MSCs produce EVs with increased levels of proangiogenic c-kit and stem cell factor (SCF). This leads to enhanced blood vessel growth in both lab experiments and living organisms [134].

Neurological disease

In an animal study on Alzheimer's disease, it was found that MSC exosomes, tiny particles, can protect brain cells in the hippocampus area. They achieve this by lowering damage caused by oxidation and preventing the breakdown of connections between nerve cells. Exosomes contain many active enzymes, such as catalases. Reducing the production of harmful molecules in brain cells, offers protection against Alzheimer's disease and other brain diseases [135]. MSC exosomes helped nearby astrocytes and neuron cells by transferring a small RNA called miR-133b. This process changed the structure of nerve fibers and improved recovery in rats that had a stroke. Exosomes from bone marrow stem cells have the potential to facilitate the growth of blood vessels and nerves while preventing the death of nerve cells. Furthermore, these exosomes reduced inflammation in the brain and helped control the harmful and overactive state of A1 astrocytes that occur after a spinal cord injury in rats. These findings suggest the potential of MSC exosomes for treating spinal cord injuries [136].

Liver injury and fibrosis

MSCs release exosomes that play a crucial role in healing liver damage and scarring. These exosomes can alter the function and appearance of liver cells. The important protective effects of MSC exosomes on the liver are primarily attributed to a small RNA called miR-223, which helps regulate the immune system and protect the liver by reducing the activity of some inflammatory genes and proteins, like cytokines, NLRP3, and caspase-1. In an animal model of autoimmune hepatitis, exosomal miR-223 blocks the NLRP3/caspase-1 signaling pathway, which is responsible for cell death (pyroptosis). This action helps decrease liver cell death and reduces inflammation in the liver. [137]. In inflamed liver tissue, the main antioxidant enzyme GPX1 helps stop the production of harmful molecules called ROS in several ways. Also, MSC-derived exosomes might help liver cells grow and prevent cell death through different mechanisms. In a study using a concanavalin A injection to induce immune system-related liver damage, MSC exosomes were found to protect the liver and reduce inflammation by lowering harmful proteins and increasing beneficial ones. The exosomes also enhanced the population of regulatory T cells, which are critical immune cells. In order to prolong the presence of MSC-derived exosomes in individuals with chronic liver disease, special PEG gels were utilized to store the exosomes and release them gradually into the bloodstream [138]. They found that using hydrogels to deliver exosomes helped them gather more scarred tissue over time compared to when exosomes were given for free. This led to better support for cell survival, less scarring, and improved healing [139]. Moreover, studies have demonstrated that MSC exosomes have the potential to promote tissue healing and enhance mobility by reducing inflammation and activating protective genes in cases of acute liver failure. Administration of MSC exosomes via intravenous delivery increased the levels of a non-coding RNA called Y-RNA-1 in the damaged tissue, protecting the injured liver [140].

The interplay of lncRNAs and exosomes in cancer

Exosomes often carry the characteristic chemical composition of cancer cells, indicating the health condition of the cell that released them. These particles, derived from various cells including cancer cells and immune cells involved in tumor response, are packed with specific materials. They are sent into the blood or other fluids in the body to send important messages. Cancer cells create exosomes to manage important functions and processes, such as their growth, division, survival, movement, the formation of new blood vessels, affecting the immune system, and resistance to treatment [141]. To escape the immune system, and facilitate the spread of cancer in specific organs, cancer cells possess the ability to modify the immune conditions in their vicinity. In this process, exosomes play a crucial role by transmitting detrimental characteristics and generating conductive areas within the body. Exosomes possess a distinct surface protein pattern that enables them to connect with specific cells. Exosomal αvβ5 integrin is related to liver cancer spread, while α6β4 and α6β1 integrins are connected to lung cancer spread [142, 143]. A recent study indicated that exosomes from aggressive pancreatic cancer cells had proteins that help cells communicate with each other, and these proteins

were expressed in different ways [144]. The interaction with cancer-causing factors in exosomes happens because of the increased production or new production of proteins and surface receptors. Exosomes are passed between support cells, immune cells, and cancer cells. DCs can be taught by tiny particles from tumors to help spread cancer to other parts of the body. Furthermore, they assist in establishing a favorable environment in the bone marrow and other areas for the original tumor cells to grow. The production of exosomes was observed to decrease when RNA interference targeted RAB27A, a protein involved in regulating membrane function and the release of exosomes in melanoma cells [145]. Tumor cells can release exosomes to help them resist chemotherapy. Research has shown that breast cancer cells and nearby cells use exosomes to facilitate resistance to radiation and chemotherapy treatments. For instance, a study by demonstrated that pre-treating tumor cells with ketotifen, an exosome release blocker, before administering doxorubicin, a chemotherapy drug, can enhance their sensitivity to the treatment. This suggests that inhibiting exosome release can potentially overcome chemoresistance in breast cancer. Furthermore, exosomes produced by tumors can be distinguished by their unique molecular markers, which may provide insights into different stages of tumor growth and progression [146–148]. These signatures can provide helpful indicators that might be useful for predicting outcomes or diagnosing conditions. Additionally, exosomes might help us predict or monitor how patients respond to treatment. You can't take biopsy samples often to check for cancer. On the other hand, liquid biopsy is a less painful method that involves checking for exosomes in body fluids. Depending on the location and type of tumor, exosomes can be extracted from various body fluids like blood, urine, spinal fluid, and saliva [149]. According to Castillo et al., analyzing the surface of exosomes through a simple test, which does not require surgery, helps scientists find cancer-related molecules. Exosomes in the bloodstream are good at carrying medicine because they can hold and deliver important molecules for a long time. Like minicells, exosomes can be used to deliver cancer treatments and important genetic materials. EnGeneIC Ltd has started using them to help target medicines for cancer care [150]. Exosomes have the ability to transmit specific RNA molecules, like small interfering RNAs (siRNAs) and miRNAs, to particular cells. Multiple studies have shown that exosomes can function in both lab settings and living organisms. In terms of targeting tumor cells, exosomes are shown to be ten times more effective than liposomes. Then efficiency of exosomes connecting with target cells is diminished when the surface proteins are cleaved. Exosomes are naturally stable, safe to use, and do not trigger an immune response. These qualities make them better than artificial drug delivery systems [151]. These qualities are highly advantageous in developing personalized treatment plans. For example, cell tropism is important for parent cells and other cancer cells to take in glioblastoma exosomes. The blood–brain barrier (BBB) is a protective barrier in the body that exosomes can go through. Using exosomes to deliver medicine improves its ability to fight lung cancer and reduces harmful side effects in other parts of the body [152]. Scientists created a special type of small RNA that targets KRAS, a gene related to pancreatic cancer, and put it into exosomes made from normal cells. These modified exosomes, called iExosomes, were shown to successfully attack KRAS in pancreatic cancer, which helps improve survival rates. It was found that when phagocytosis of exosomes happens and it reduces CD47, more iExosomes stay in the body. The genetic makeup of exosomes can change based on things like the social support given to cancer patients. This brings up the interesting thought of using exosomes to improve personalized treatment [153]. LncRNAs are involved in both stopping tumors and helping them grow. lncRNA SPRY4-IT1 helps bladder cancer grow by acting like a sponge that absorbs miR-101-3p. This action boosts the production of EZH2, which promotes the cancer cells to multiply and spread [154]. On the other hand, ANCR is a type of RNA that helps prevent tumors by getting rid of EZH2, which helps lower the spread and invasion of breast cancer. LncRNAs are more specific to certain tissues than protein-coding mRNAs, and they are made in large amounts in cancer cells. As a result, the levels of lncRNA expression are a better marker because they are closely related to the features of cancer [155]. LncRNAs demonstrate unique patterns in primary tumors and metastases, similar to miRNAs, and play important roles in regulating cancer-related pathways. These levels are carefully regulated in response to environmental stressors and signals that may damage DNA. Antisense oligonucleotides (ASO), hammerhead ribozymes, aptamers, small molecules, and siRNAs can all block the action of lncRNA. Targeting these lncRNAs could also help improve cancer treatment [156]. By binding to harmful lncRNAs in a manner that corresponds to their structure, small molecule medications can effectively block their activity. Researchers suggest that lncRNA ASBEL could be a new target for treating triple-negative breast cancer. It has been shown that an anti-ASBEL ASO can reduce ASBEL levels, which in turn increases the amount of the protein BTG3 that helps stop cell growth. Like this, a specific ASO

lowers the levels of Malat1 lncRNA in a mouse model of breast cancer, which stops the cancer from spreading [157]. To enhance the effectiveness of chemotherapy and halt the spread of ovarian and breast cancer cells, a new treatment called anti-lncRNA peptide nucleic acid has been developed. Investigating the mechanisms of lncRNAs is crucial for understanding their roles in cancer. Currently, ASOs are the best method for studying lncRNA function and developing lncRNA-based cancer treatments. However, novel approaches utilizing CRISPR, such as CRISPRi to decrease lncRNA activity or CRISPRa to increase it, offer powerful and distinct avenues for exploring the functions of lncRNAs [158] (Table 3).

So, Fig. 3 shows how exosomes from tumors help in spreading tumors to other parts of the body. Exosomes from tumors help the spread of cancer in different ways. These tiny particles come from cancer cells and can affect

Table 3 Exosomal lncRNAs in cancers

Exosomal lncRNA	Exosomal lncRNA	Function in cancer	Refs.
MIAT	MIAT	Promote breast cancer progression	[159]
HULC	HULC	EMT, migration, invasion	[160]
FAM225A	FAM225A	Proliferation, migration, and invasion	[161]
LINC01133	LINC01133	Cell survival, proliferation, EMT	[162]
CCAT1	CCAT1	Migration, tube formation	[163]
CEBPA-AS1	CEBPA-AS1	Apoptotic cell death	[164]
CRNDE-h	CRNDE-h	Th17 polarization	[165]
LINC02418	LINC02418	Cell survival, proliferation	[166]
HOTAIR	HOTAIR	Accelerates the development modulating BCL2 and targeting miR-143-3p	[167]
MALAT1	MALAT1	Accelerates Cervical Carcinoma Proliferation by Suppressing miR-124 Expression in Cervical Tumor Cells	[168]
MEG3	MEG3	Cell proliferation and apoptosis by regulating miR-21	[169]
DLX6-AS1	DLX6-AS1	Proliferation, migration, EMT, anti-apoptosis	[170]
LINC01133	LINC01133	Proliferation, migration, invasion	[171]
MALAT1	MALAT1	Migration, invasion, metastasis	[172]
KCNQ1OT1	KCNQ1OT1	PD-L1, immune evasion, proliferation, apoptosis, migration, invasion, metastasis	[173]
MALAT1	MALAT1	Critical Regulator of the metastasis phenotype	[174]
LINC00161	LINC00161	Angiogenesis, metastasis	[175]
JPX	JPX	Metastasis and chemoresistance of cancer	[176]
KCNQ1OT1	KCNQ1OT1	Proliferation, viability, survival, apoptosis, migration, invasion, metastasis, oxaliplatin, and sorafenib resistance	[177]
FAM72D-3	FAM72D-3	Apoptotic cell death	[178]
TUC339	TUC339	M2 polarization, EMT, pro-inflammatory cytokines	[179]
SNHG14	SNHG14	Promotes chemoresistance to trastuzumab	[180]
H19	H19	Promotes tumorigenesis, metastasis, and angiogenesis of bladder cells	[181]
MALAT1	MALAT1	Paclitaxel resistance, proliferation, migration, stemness, metastasis	[182]
PCAT-1	PCAT-1		[183]
SPRY4-IT1	SPRY4-IT1		[184]
UCA1	UCA1	Metastasis	[185]
UCA1-201	UCA1-201		
UCA1-203	UCA1-203		
LINC00355	LINC00355		[186]
ANRIL	ANRIL	Paclitaxel resistance	[187]
PCAT-1	PCAT-1		[188]
FAM225A	FAM225A	Cell survival, EMT	[189]
LINC01711	LINC01711	Proliferation, migration, invasion	[190]
ZFAS1	ZFAS1		[191]
FMR1-AS1	FMR1-AS1	Cell survival, invasion, stemness	[192]
POU3F3	POU3F3	Transition into CAFs, cisplatin resistance	(193)

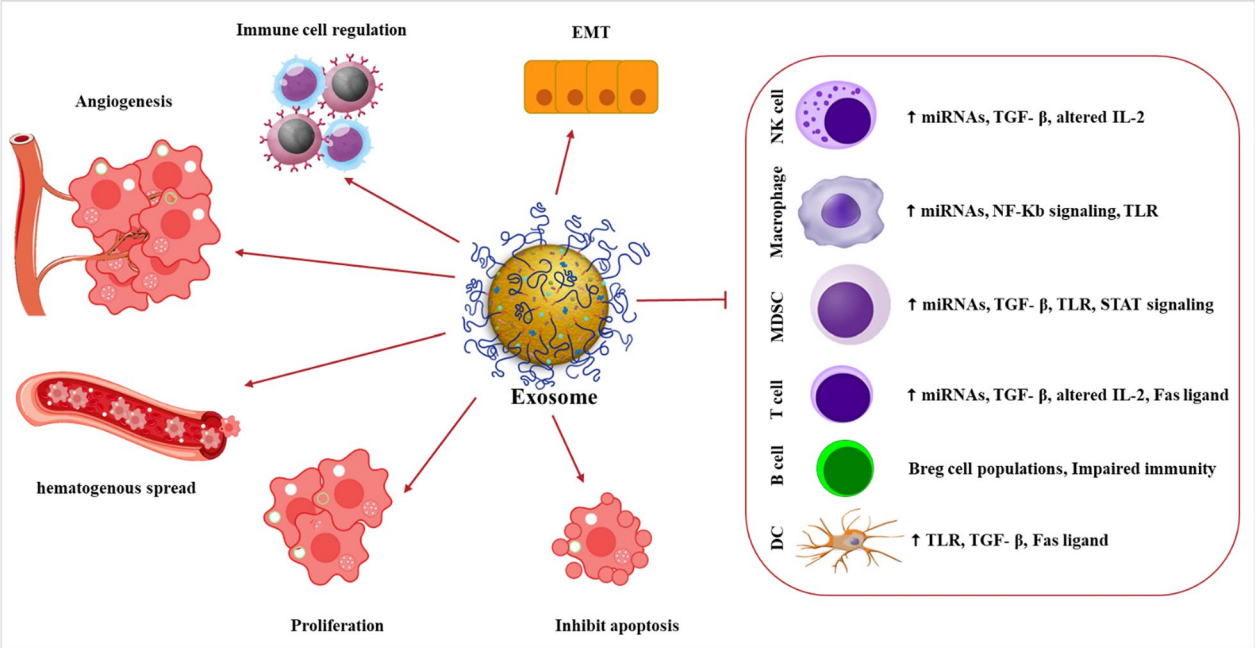


Fig. 3 Exosomes from tumors help cancer spread. Exosomes from tumors help with the spread of cancer in many ways

other cells far away, helping cancer spread and grow new tumors. Tumor-derived exosomes can help cancer spread by encouraging the growth of new blood vessels, making tumor cells move and invade more easily, weakening the immune system, and helping to create spots in the body where cancer can grow before it spreads. It's important to know how tiny particles from tumors help cancer spread to create better treatments that stop this process and help patients feel better.

Exosomal lncRNAs: signs and helpers in cancer growth

Cancer subtypes, biomarkers, and conceivable treatment targets can all be found using exosomal lncRNA profiling. One well-known lncRNA biomarker is PCA3, which is extricated from a patient's pee and is more exact at identifying prostate cancer than the habitually utilized prostate-specific antigen. PCA3 has as of now had a part of clinical success [194]. In addition to PSA, a small piece of lncRNA called MALAT1-derived miniRNA (MDminiRNA) can be used as a blood test marker to find prostate cancer. Exomal lncRNAs HOTAIR, MALAT1, and MEG3 from cervical cancer show promise as markers for the disease [195]. Scientists recently found a special group of long non-coding RNA (lncRNA) in the blood that can help tell apart patients with clear cell kidney cancer from healthy individuals. Researchers suggest that a type of RNA called ZFAS1, found in exosomes, could help diagnose and predict gastric cancer because it plays a role in the disease's progression [196]. Exosomal MALAT1 could be a useful and easy way to check for non-small cell lung cancer using a blood test. The amount of this substance in the blood of patients is associated with the disease is and whether it has spread to the lymph nodes. It's interesting to know that MALAT1 found in exosomes is also linked to the development of breast cancer [197]. Exosomal lncRNA 91H might be a helpful early indicator found in blood tests for the return and spread of colorectal cancer. Patients with high levels of this molecule are more likely to develop new tumors [198]. Bladder cancer can be detected and the likelihood of recurrence can be predicted using MEG3, SNHG16, and MALAT1, which outperform urine samples. RNA sequencing reveals that HOTAIR, HYMA1, OTX2-AS1, LINC00477, and LOC100506688 are found in high amounts in urine exosomes of bladder cancer patients, according to RNA sequencing [199]. Research shows that exosomes have the most lncRNAs found in the blood, based on studies of three types of serum extracellular vesicles (EVs). A marker that aids in diagnosing colorectal cancer has been haves been put together to create a marker that helps diagnose colorectal cancerdeveloped by combining two mRNAs and one long non-coding RNA (BCAR4) [200]. Bioinformatics analysis shows that certain long non-coding RNAs (lncRNAs) that can interact with microRNAs (miRNAs) are more common in prostate cancer and liver cancer. FAL1 has been shown to absorb miR-1236 in this case, which helps liver cancer cells grow and move more [201]. The levels of RNA messages found in

exosomes, including long non-coding RNAs (lncRNAs), match how much of these messages are made in the original cells. Some lncRNAs are more likely to be included in exosomes than others. When looking at different liver cancer cell lines, we found that certain long, non-coding RNAs (lncRNAs), especially TUC339, were much more present in exosomes. This suggests that there are special ways these lncRNAs are packed for export. The growth of liver cancer cells was decreased when TUC339 was blocked using siRNA in those cells. This shows that tumor cells can share their genetic material with other cells through exosomes that carry a type of RNA known as lncRNA [202]. Another study found that when the amount of the lncRNA growth arrest-specific 5 (GAS5) in cells resulted in a significant increase in the presence of GAS5 in exosomes. In disease conditions such as cancer, the transportation of lncRNAs by exosomes differs from normal conditions. This difference includes both the quantity and types of lncRNAs being transported [203]. LncRNAs found in tumor-derived exosomes can alter the function of other cells tumor-derived exosomes can alter the function of other cells promoting faster growth, resistance to chemotherapy, prolonged cell survival, or changes in immune system reactions. For example, two studies have shown that exosomes can carry specific molecules, linc-VLDLR, and linc-RoR, which can change how sensitive liver cancer cells are to chemotherapy [204]. Hepatocellular carcinoma gets worse when tumor cells help other cells survive low-oxygen conditions by sending out exosomes that contain linc-RoR. Exosomes released from primary tumors carry a harmful RNA called UCA1. These exosomes help bladder cancer grow and spread in their surrounding environment [205]. Another study showed that the transfer of UCA1 through exosomes helped breast cancer cells resist tamoxifen treatment. Similarly, the presence of exosomes carrying lncARSR makes advanced kidney cancer more difficult to treat analogous to how resistance to Sunitinib facilitates tumor growth [206]. Exosomal lncRNAs are a way for tumor cells to change the nearby cells, helping cancer to spread and avoiding detection by the immune system. Glioma cells can release exosomes that are rich in a type of RNA called POU3F3. These exosomes help to promote the growth of new blood vessels [207]. Exosomes that have a lot of lncRNA CCAT2 give similar results. Exosomes help create a supportive environment in the bone marrow of people with acute myelogenous leukemia by carrying both coding and noncoding RNAs into nearby cells. Another study found that exosomes from ovarian cancer can help endothelial cells move better from a distance. They do this by sending lncRNAs that were stopped by exosomes from immune cells linked to the tumor [208]. Even though there could be advantages, using exosome-mediated lncRNAs for therapy is still primarily under investigation. Some specific long non-coding RNAs (lncRNAs) identified in subsequent treatments have been found to inhibit tumor growth. For example, the tumor suppressor lncRNA GAS5 induces cell death, retards cell proliferation, and reduces energy utilization. Utilizing exosomes as a vehicle may enhance the delivery of particular lncRNAs that combat tumors, offering a potential avenue for cancer treatment [203]. Cells that release tiny packages called EVs can be changed using genes to show special markers that help them deliver medicine directly to cancer cells. However, there hasn't been a description of using these tiny packages to target specific long RNA molecules yet. There are many challenges with lncRNAs in exosomes that need to be solved. For example, we need to figure out the roles of lncRNAs and how they relate to certain cancers by using computer analysis and experiments. One major problem is that we don't have precise ways to start or stop the release of certain types of EVs without affecting other kinds of EVs. To compare results from different patients, groups, and labs, we need to make sure that the ways we create and measure exosomal lncRNAs from body fluids are consistent in clinical settings. We need to set up global standards and lab approval processes before using this in hospitals [209, 210]. Figure 4 shows how exosomes can be important indicators for detecting cancer. The image shows the idea of liquid biopsies, which are tests that look at the molecular materials in exosomes. These materials include DNA, RNA, proteins, fats, and other small molecules. This analysis provides special chances to understand the details of tumors and helps in diagnosing them. The picture highlights how exosomes can carry important information that helps us understand cancer better at a tiny level.

Exosomes in cancer immunotherapy

Main treatments like chemotherapy and radiation don't work well for some cancers and can cause serious side effects. Newer treatments like immune checkpoint inhibitors, anti-CTLA4, and anti-PD1/PDL1 have changed how these cancers are treated [211]. These powerful treatments enhance the patient's immune system, enabling immune cells, especially CD8 + T-cells, to effectively combat tumors. While these therapies have proven beneficial, there is still significant room for improvement. Immune checkpoint therapies may have limited efficacy and may also trigger autoimmune issues. Factors such as genetics and biology can make it challenging for some patients to respond well to these treatments. To solve these problems, we need new methods that are less harmful and work better for a longer time. One type of treatment uses exosome called nanoparticles, especially

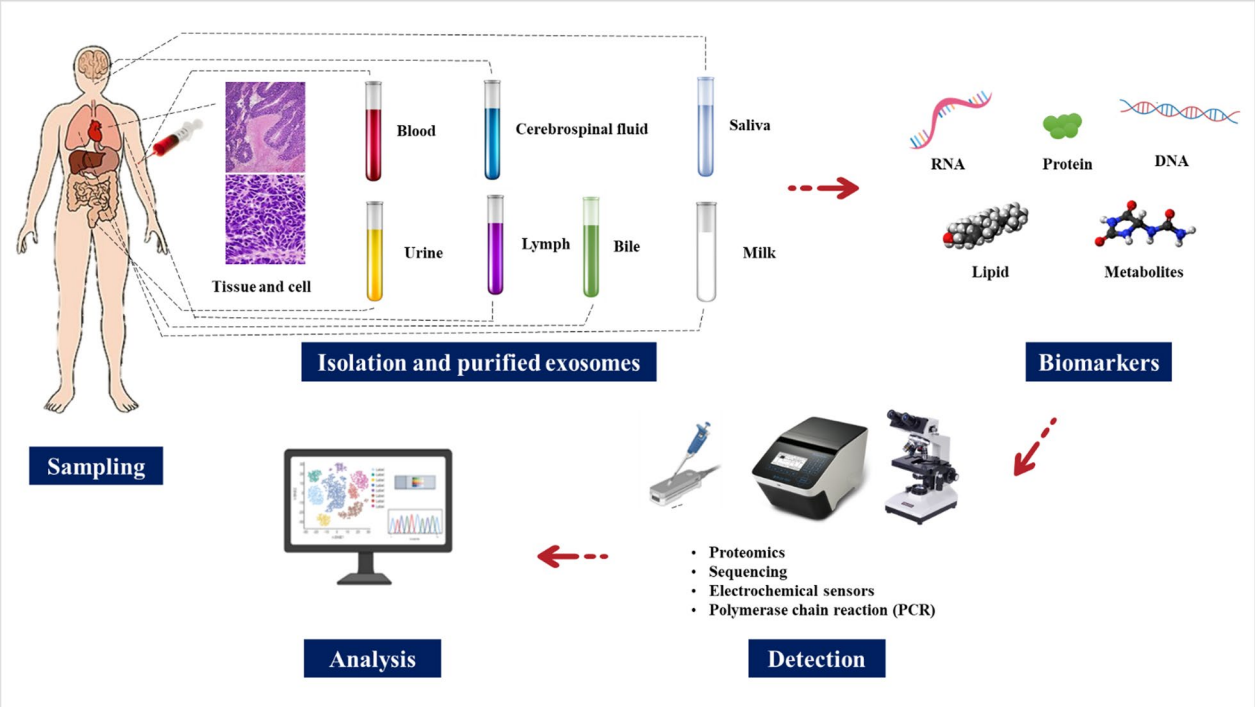


Fig. 4 Exosomes can be used to help find cancer. In liquid biopsies, looking at the molecules in exosomes like DNA, RNA, proteins, fats, and small chemicals can offer great opportunities to learn about the details of tumors and help with diagnosis

exosomes [17]. In the past few years, new ways to deliver medicines and vaccines, like liposomes, niosomes, and different kinds of metal particles, have been developed. These systems help to accurately target tumors either directly or in different ways. The main goal of cancer immunotherapy is to help the immune system recognize and get rid of cancer cells. By focusing on DCs and macrophages, these particles can help boost the immune system by delivering substances that stimulate it and help recognize invaders [212]. This allows the body's natural defense system to find many types of tumor markers, present them effectively, get the help needed, and successfully activate CD4+ and CD8+ T cells. Even though nanoparticles are often used in many drug formulas, these nanoparticle-drug combinations have certain problems in both medical use and development. Problems like not knowing if they are safe for a long time and not being able to accurately target the right cells make it hard to use nanoparticles in treatments [213]. For instance, exosomes derived from autologous breast cancer cells were utilized to develop siS100A4 nanoparticles coated with an exosomal membrane. To assess drug transport, biocompatibility, and protection against siRNA degradation, cationic bovine serum albumin (CBSA) was conjugated to the exosomes. The results demonstrated that the CBSA-conjugated siS100A4 exosome effectively inhibited postoperative breast cancer by silencing genes that either promote or hinder the growth of breast cancer cells [214]. Figure 5 shows how using exosomes could help treat cancer. The diagram shows different methods, such as delivering drugs directly to specific places, stopping the creation, release, and absorption of exosomes, and using exosomes in immune treatments. These methods show potential for accurate and effective cancer treatment by sending medicine straight to tumor areas, blocking the making and release of tumor-related exosomes, and using the immune-boosting abilities of exosomes.

Even after years of research, cancer treatment using tiny particles to boost the immune system still faces challenges in biology, technology, and hospital studies. However, there have been promising developments with a special type of exosomes, which have shown encouraging results. This is significant because we can modify the cells that produce exosomes to change what they carry and where they go, making it easier and more precise to target specific areas. Exosomes, which carry important cargo and play a role in various biological processes, can be utilized to deliver drugs, proteins, and genes, making them potentially valuable in immune therapy for cancer treatment. One advantage of exosomes over other tiny particles is that they remain in the body for longer periods of time, naturally finding their targets and posing

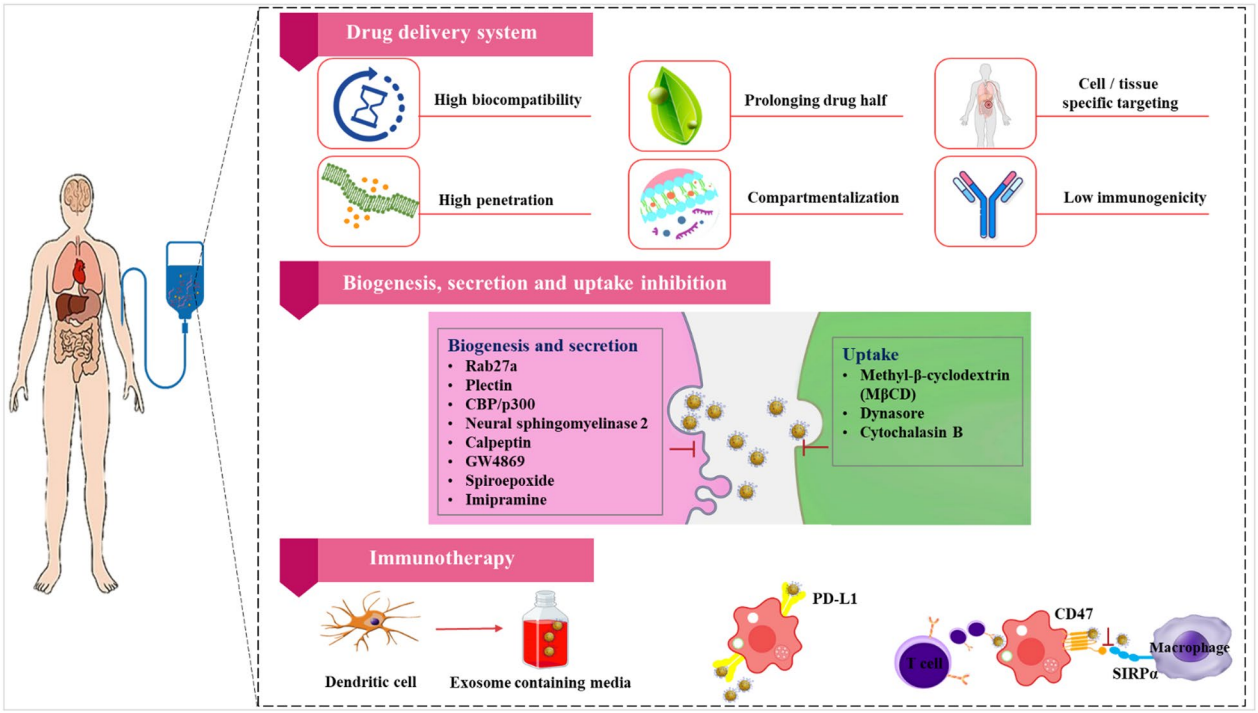


Fig. 5 Exosome therapies can help treat cancer by delivering drugs directly to tumor areas. This includes blocking the production, release, and absorption of exosomes. Immunotherapy can also be used for cancer treatment

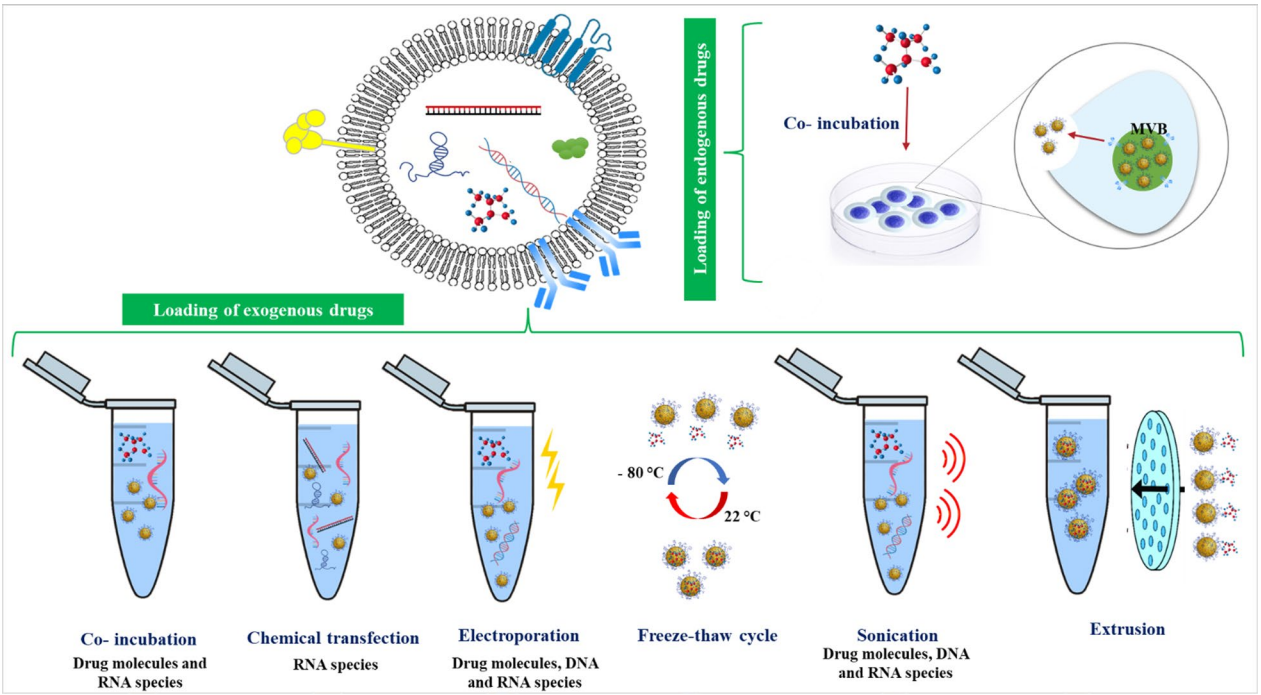


Fig. 6 Different ways to load cargo into exosomes, either before or after they are made

a low risk of harmful effects [215]. Figure 6 illustrates the various techniques employed to load cargo into exosomes, both preloading and post-loading methods. Preloading involves incorporating specific materials into the main cells prior to exosome formation, ensuring their inclusion within the exosomes upon creation. On the other hand, post-loading techniques involve directly introducing cargo into exosomes after their generation. These loading methods enable the packaging of diverse materials such as DNA, proteins, medicines, or imaging substances into exosomes, facilitating targeted delivery and treatment applications. Consequently, these loading methods enhance the versatility of exosomes in carrying a wide range of materials for various medical purposes.

Exosomes have shown potential for helping with various health issues in early research. Exosomes were effectively used to transport catalase across the blood–brain barrier in Parkinson's disease, which made the patient's condition better [216]. Exosomes can be made using a similar method to safely deliver medicines and immune treatments across the BBB in patients with brain tumors (gliomas) or cancer that has spread to the brain. To aim at specific types of cells, exosomes were modified by altering their surface and then filled with different immune-boosting drugs. The study focused on how chronic myeloid leukemia (CML) cells have more IL-3 receptors (IL3-R) than healthy immune cells [217]. Interleukin 3 (IL-3) and a protein called Lamp2b, which comes from exosome in cells, were created to be active in human kidney cells known as HEK293T. The BCR-ABL siRNA or imatinib, which stops CML cells from growing in lab settings and living organisms, was also included in these exosomes. Different types of cancer, like melanoma that shows the epidermal growth factor receptor (EGFR), can be treated in similar ways. Exosomes, made from cells that have been modified to produce special proteins (VEGF and LAMP2b), can effectively find and attach to melanoma cells. Natural killer (NK) cells have been shown to effectively combat tumors in mouse models. Exosomes derived from DCs have been demonstrated to enhance NK cell activation and proliferation by upregulating IL-15Ra and NKG2D expression. These DC-derived exosomes were shown to contain functional IL-15Ra and NKG2D ligands, suggesting a direct mechanism for NK cell activation. This finding is consistent with the broader concept of harnessing NK cells for cancer immunotherapy, as highlighted by Maskalenko et al. [218, 219]. Furthermore, Chan et al. have systematically reviewed the potential of NK cell-derived extracellular vesicles as a promising immunotherapeutic strategy. These studies collectively underscore the significant role of exosomes in modulating NK cell function and provide a strong rationale for further exploring their therapeutic potential in human cancer. By promoting NK cell growth, activation, and IFN-γ production, exosomes could serve as a novel immunotherapeutic approach for cancer treatment [220]. Others have used exosomes from DC to treat human breast cancer cells called SK-BR-3 [221]. They activated CD3 + T-cells that had already been exposed to SK-BR-3 antigens using these tumor cells. T-cells that encountered tumor cells treated with DC-derived exosomes exhibited a significantly higher number of cells producing IFN compared to T-cells exposed to untreated tumor cells. These results demonstrate that tumor cells are more efficient at activating T-cells when they internalize DC-derived exosomes. The exosomes produced by peptide-pulsed DCs play a crucial role in the immune system by presenting fragments of pathogens to T-cells. This indicates that exosomes derived from dendritic DCs possess MHC-peptide structures and co-stimulatory molecules on their surface, enabling them to effectively transport antigens. Furthermore, exosomes derived from mouse cells containing a specific tumor protein, human mucin 1 (hMUC1), induced a robust immune response and aided in combating the growth of tumors expressing this protein in living organisms [222, 223]. They turned on CD3 + T-cells that had already met SK-BR3 proteins using these tumor cells. T-cells that came into contact with tumor cells treated with DC-exosomes made a lot more IFN compared to T-cells that were with untreated tumor cells. These results show that tumor cells were more effective at activating T cells when they received DC-exosomes. The exosomes generated by specialized cells called dendritic cells assist the immune system by presenting fragments of pathogens to T-cells. This implies that dendritic cell-produced exosomes possess MHC-peptide structures and co-stimulatory molecules on their surface, which enhances their capacity to transport antigens effectively. Interestingly, small vesicles from mouse cells containing a specific tumor protein known as human mucin 1 (hMUC1) triggered a potent immune response and contributed to the suppression of tumor growth in living organisms [224, 225]. In lab tests, splenocytes grown alongside DCs showed more growth and released more IL-2. B16F1-CIITA exosomes made more mRNA for inflammatory substances, such as TNF-α, IL-12, and the chemokine receptor CCR7, compared to exosomes from B16F1. Also, B16F1-CIITA-exosomes slowed down tumor growth in a way that depended on how much was given. Mice that received B16F1-CIITA-exosomes had higher amounts of IgG2a antibodies, IFN-γ, and CD8 + T cells that are specific to TRP2. These results suggest that MHC class II tumor exosomes are important for cancer treatment because they work better at helping the immune system fight tumors compared to regular exosomes. As a result, like DCs, the exosomes

that come from DCs are full of important substances and signals needed to show antigens and activate T-cells. These molecules, like CD40, CD80, CD86, and MHC class I and II, help wake up the body's immune system, both the quick response and the long-term response, so it can fight tumors better [226, 227]. Exosomes have shown good results in lab tests and early research. Clinical trials also suggest they could be helpful as immune system treatments. One of the best ways to fight cancer is to target cancer stem cells. Exosomes from the patient's immune cells were used to treat patients with advanced melanoma in early-stage clinical trials. The exosomes had either MHC type I or type II, along with MAGE tumor markers, depending on the MAGE peptide. Even though the results about how well it works were not clear, it was shown that giving exosomes helps [23].

Exosomes for delivering medicines made of RNA or DNA

Due to their large size and negative charge, therapy genes that are not protected cannot easily penetrate cell membranes, making it difficult for cells to uptake them [228]. Additionally, unprotected genes can be rapidly degraded by nucleases, rendering them ineffective in reaching their target cells. Therefore, the development of gene delivery tools is crucial for successful gene therapy. Both viral and non-viral carriers have been created to deliver genes, but they have significant drawbacks, such as causing high toxicity throughout the body and triggering immune responses [229]. Exosomes are better at carrying genes because they are safe for the body, do not cause immune reactions when given properly, and can reach their intended targets effectively. Therapeutic materials can be added to exosomes after they are separated, or they can be put into the cells that create exosomes before being packaged into them to carry genetic information [230]. For example, before collecting exosomes, the donor cells were modified with a special mRNA/protein called CD-cytosine deaminase; UPRT-uracil phosphoribosyl transferase; and EGFP-enhanced green fluorescent protein (CD-UPRT-EGFP). These exosomes, along with a medication called 5-fluorocytosine (5-FU), were administered to schwannoma cells. The enzymes CD and UPRT then converted the medication into the active anti-cancer drug, 5-FU [231]. To enhance targeting, the exosomes were modified to display a membrane protein called Lamp2b, which was fused with a rabies virus protein (RVG) peptide. In this way, the effect of different viruses may have a negative impact on the performances of exosomesThese RVG exosomes were purified, loaded with siRNA, and tested both in the laboratory and in living organisms. The results demonstrated that exosomes can traverse the blood–brain barrier and effectively deliver siRNA treatment to the brain without triggering significant immune responses or causing harmful side effects, even after repeated use [232, 233].

Besides, a recent study showcased a novel approach for targeted RNA degradation using engineered exosomes. By fusing the RNA-binding protein HuR to the C-terminus of Lamp2b, a lysosomal membrane protein, researchers created a chimeric protein that could be incorporated into exosomes. These engineered exosomes effectively delivered HuR to target cells, where it facilitated the lysosomal degradation of specific RNA molecules, especially under acidic conditions. This strategy proved particularly efficient in macrophages, cells that are known to be resistant to conventional RNA interference methods due to their abundant lysosomes. In a mouse model of liver injury, acidified exosomes containing the HuR-Lamp2b fusion protein significantly reduced liver fibrosis and downregulated the expression of miR-155 and other inflammatory genes. These findings suggest that exosome-mediated lysosomal clearance could offer a promising new strategy for manipulating gene expression in vivo [234].

Exosomes for medicine delivery

The most common ways to put drugs into tiny capsules are by heating, using sound waves, and applying electric energy. In a study, researchers placed a cancer drug called paclitaxel (PTX) inside exosomes that were made by immune cells called macrophages (exoPTX). The findings showed that using sound waves (sonication) was the best method for loading the drug into them. Also, exoPTX showed that it gathers more in cancer cells and helps reduce the spread of cancer compared to liposomes and other similar carriers made from polymers [235]. To reduce immune reactions and side effects, exosomes were made in young dendritic cells. The iRGD-Lamp2b plasmid was introduced into the cell lines to make the Lamp2b protein, which is found on exosomes. This protein is linked to a special iRGD peptide that targets specific cells better [236]. Combining iRGD-Lamp2b plasmids with drug delivery could be a great way to get drugs to tumors more effectively. While we know it helps, explaining exactly how it works would make our argument even stronger. As highlighted, the iRGD peptide exhibits a remarkable ability to selectively target tumor vasculature and penetrate deep in to tumor tissue [237]. The peptide can target tumors better because it sticks strongly to integrins, which are proteins in the blood vessels in tumors. Plus, it can also bind to neuropilin-1, a receptor that is often more active in cancer cells. This ability to bind to both helps drugs attached to this peptide collect in tumors, leading to better treatment results [238].

The combination of iRGD with Lamp2b, a lysosomal membrane protein, offers additional advantages. Lamp2b is known to be overexpressed in many cancer types and is involved in various cellular processes, including antigen presentation and autophagy. By fusing iRGD to Lamp2b, the resulting construct may exhibit improved intracellular trafficking and delivery of therapeutic agents to lysosomes, where they can exert their effects. This could potentially enhance the overall efficacy of the drug delivery system [239].

After being cleaned, Dox was put into exosomes and then given to breast cancer cells in the lab. The research shows that changed exosomes can deliver Dox only to tumor areas, helping to stop tumor growth while making it less harmful and less likely to cause immune reactions [240]. Curcumin, a natural compound found in turmeric, possesses anti-inflammatory and anti-cancer properties. It is frequently employed in treatments and can be encapsulated in exosomes for enhanced delivery. Exosomes derived from EL-4 mouse cancer cells were combined with curcumin during a centrifugation process involving layers of sugar water. This resulted in the production of Exo-cur, which rendered curcumin more stable and easier for the body to utilize. Mice treated with a combination of curcumin and exosomes demonstrated improvement in a severe condition caused by lipopolysaccharide (LPS) [241, 242]. Considerable efforts have been made to utilize exosomes as specialized delivery vehicles for medication. However, future research must address significant challenges. Firstly, the absence of standardized methods for extracting and purifying exosomes complicates this field of study. Conventional methods of isolation, such as ultracentrifugation, are time-consuming and often result in the mixing of exosomes with other small particles [243]. This process takes a long time, and the exosomes made often get mixed up with other small particles. Having non-exosomal EVs will lower the effectiveness of treatments because exosomes are important for properly delivering drugs and genes [244]. Establishing a rapid and reliable method for separating exosomes is a key objective of current research. Additionally, careful consideration must be given to the source of exosomes for specific applications. Exosomes derived from cancer cells should not be used in cancer treatments due to the potential presence of substances that could accelerate disease progression. Although exosomes can be generated by various types of human cells, their impact on the efficacy of exosome-mediated delivery remains unclear [245]. Exosomes need to be carefully studied and defined before they can be used as treatment options. Finally, even when using the same donor cells, exosomes obtained from cell cultures may exhibit variations in quality. The current limitations of cell cultivation and exosome purification methods hinder the widespread and consistent production of exosomes. Therefore, the development of large-scale, efficient, and cost-effective methods for exosome production is imperative [246]. Exosomes look very promising for medical uses, in short. But some basic problems need to be solved to make progress in this area. One of the biggest challenges is finding reliable and effective methods for separating and identifying things [247]. While exosomes hold immense promise for clinical applications, several challenges must be addressed before their widespread use. Quality control remains a significant hurdle, as the heterogeneity of exosomes derived from different cell sources can lead to variability in their composition and biological activities [248]. Standardization of production methods is also crucial to ensure consistent exosome preparations. Moreover, the therapeutic efficacy of exosomes can vary depending on factors such as the origin of the donor cells, the isolation method, and the cargo loaded into the exosomes [249]. For instance, findings demonstrated that exosomes derived from mesenchymal stem cells exhibited varying levels of immunomodulatory activity when isolated using different ultracentrifugation protocols. Additionally, the potential immunogenicity of exosomes, especially when derived from allogeneic sources, must be carefully considered to minimize adverse effects [250]. To address these challenges, the development of robust and reproducible methods for exosome isolation, characterization, and quality control is essential. Furthermore, rigorous preclinical and clinical studies are required to establish the safety and efficacy of exosome-based therapies.

Conclusion

The various pro-tumorigenic effects of exosomes are receiving more recognition. Cancer patients have more exosomes in their blood than healthy people, and this amount goes up as the cancer gets worse. This suggests that exosomes from tumors can help tumors grow in cancer patients. Cancer cells use exosomes to harm the immune system, the area around them, and other parts of the body. This helps them survive, grow, and spread. Because exosomes were only recently discovered and studied, we do not fully understand how they work in cancer. In cancer, there are special cells called cancer-initiating cells. These cells can cause tumors to grow and can lead to the return of tumors both nearby and in other places in the body. Regular cancer treatments that only aim at killing the current cancer cells have a hard time because some cancer cells can grow back and change into different types of cells. Many studies have looked into the biological traits of CSCs and the substances they release. The goal is to create treatments that can specifically attack CSCs. This shows how important exosomes

are for helping cells talk to each other and creating a special environment that keeps a balance between CSCs and other cancer cells. Because of this, CSCs are a good target for trying to disrupt that balance. More studies are needed to fully understand how CSC-Exosomes affect cancer growth, spread, and the immune response to cancer. Exosomes also act as carriers for tumor cells to send signals to nearby cells, themselves, other parts of the body, and the immune system. We still don't fully understand how exosomes work, and research on the potential medical uses of exosomes from MSCs is just starting. More and more evidence shows that exosomes help tumor cells by carrying important signals. This helps them communicate with their surroundings, the immune system, and even other parts of the body. This way of cell-to-cell communication can make tumor cells more aggressive and resistant to treatments. It can also affect nearby cells to help the tumor grow, weaken the immune system, and create areas in the body ready for the spread of cancer. To fully understand how exosomes work, especially the lncRNAs they carry, it is important to know what these tiny packages contain. This knowledge helps us figure out how they send signals and cause different effects. Studying exosomes offers a new way to find cancer and track changes during cancer growth and treatment. Exosomal lncRNAs that are found in the bloodstream could greatly improve how we diagnose and predict diseases. They are found a lot in human body fluids and allow for quick tests that don't need surgery or only need a little bit of it. Also, they might be possible targets for treating diseases in the future. Bioinformatics tools that study lncRNA sequencing, structure, and possible functions help us understand how lncRNAs work in EVs and cell-to-cell communication. We can use systems biology methods to understand how cells communicate with each other through exosomes and to see what happens if we interrupt this communication. Also, computer methods like machine learning can be used to guess how lncRNAs might work and how they are connected to diseases like cancer.

Future perspectives and research directions

While significant strides have been made in understanding the intricate role of exosomes in cancer biology, numerous avenues remain to be explored. A deeper comprehension of the precise molecular mechanisms underlying exosome-mediated modulation of the tumor microenvironment is imperative. This includes elucidating the specific signaling pathways activated by exosomal cargo and characterizing the heterogeneity of exosomes within and between tumors. Furthermore, the intricate interactions between exosomes and various immune cell types, such as T cells, B cells, and macrophages, warrant further investigation. The phenomenon of exosomal mimicry of antigen-presenting cells, leading to immune tolerance, also requires additional research. In terms of therapeutic implications, the development of efficient methods for producing, targeting, and immunomodulating exosomes is crucial. Moreover, exploring the combination of exosome-based therapies with conventional treatments holds immense promise. In summary, addressing these research gaps will not only expand our knowledge of exosome biology but also pave the way for the development of novel and effective cancer therapies.

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Author contributions
AZT and SV were involved in the primary methodology section and also wrote the primary draft of the manuscript. SEN was accompanied by technical and editing actions of the manuscript. AN, KB, and EB were involved in different parts of this manuscript. In this way, AAS was involved as a supervisor in all sections of the manuscript including conceptualization, writing, reviewing and also editing. All the authors studied the final version of the paper and acknowledged it.

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No datasets were generated or analysed during the current study.

Declarations

Competing interests
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