

Review

Stem Cell-Derived Exosomes: Non-Coding RNA Cargos for Reprogramming the Tumor Immune Microenvironment

Manal Hadi Ghaffoori Kanaan ^{1, *}, Beom-Jin Lee ^{2, 3}, Sura Saad Abdullah ², Chulhun Park ⁴, Abdolmajid Ghasemian ⁵, Steward Mudenda ⁶

1. Department of Food Industries/Technical Institute of Suwaria, Middle Technical University, Baghdad, Iraq; E-Mail: dr.manalhadi@mtu.edu.iq; ORCID: 0000-0002-9409-4778
2. College of Pharmacy, Ajou University, Suwon 16499, Republic of Korea; E-Mails: bjl@ajou.ac.kr; surasaad@ajou.ac.kr
3. Research Institute of Pharmaceutical Sciences and Technology, Ajou University, Suwon 16499, Republic of Korea
4. College of Pharmacy and Jeju Research Institute of Pharmaceutical Sciences, Jeju National University, Jeju 63243, Republic of Korea; E-Mail: chpark@jejunu.ac.kr
5. Non communicable Diseases Research Center, Fasa University of Medical Sciences, Fasa, Iran; E-Mail: majidghasemian86@gmail.com
6. University of Zambia, Department of Pharmacy, School of Health Sciences, Lusaka, Zambia; E-Mail: freshsteward@gmail.com

* **Correspondence:** Manal Hadi Ghaffoori Kanaan; E-Mail: dr.manalhadi@mtu.edu.iq; ORCID: 0000-0002-9409-4778

Academic Editor: Masahiro Sato

OBM Genetics
2026, volume 10, issue 1
doi:10.21926/obm.genet.2601325

Received: October 10, 2025
Accepted: January 08, 2026
Published: January 14, 2026

Abstract

Stem cell-derived exosomes (SDEs) have emerged as revolutionary mediators in cancer immunotherapy, offering unprecedented potential to reprogram the immunosuppressive tumor immune microenvironment (TIME). These nano-sized extracellular vesicles, laden with non-coding RNAs (ncRNAs), serve as natural biocompatible carriers, capable of orchestrating immune cell dynamics, stromal remodeling, and tumor cell fate. Unlike their tumor-derived counterparts, which often propagate oncogenic signals, SDEs uniquely harbor



© 2026 by the author. This is an open access article distributed under the conditions of the [Creative Commons by Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium or format, provided the original work is correctly cited.

immunomodulatory miRNAs (e.g., miR-155, miR-342-3p) and lncRNAs (e.g., MALAT1, XIST) that recalibrate TIME components, activating cytotoxic CD8⁺ T cells, polarizing macrophages toward anti-tumor M1 phenotypes, and suppressing regulatory T cells (Tregs). This review delineates how SDEs leverage ncRNA cargo to dismantle immunosuppressive barriers: by silencing checkpoint molecules (PD-L1), reversing chemoresistance, and rewiring cancer-associated fibroblasts (CAFs). We highlight the dual roles of exosomal ncRNAs, such as miR-126, which initially bolster cancer stemness but, upon sustained delivery, trigger tumor-selective necroptosis, underscoring their context-dependent therapeutic utility. Despite promising preclinical outcomes, challenges in scalable production, off-target effects, and tumor heterogeneity necessitate engineered solutions, CRISPR-edited exosomes, surface-targeted modifications, and combinatorial regimens with checkpoint inhibitors. By integrating mechanistic insights with translational advances, this review positions SDEs as a paradigm-shifting tool in precision oncology and advocates for multidisciplinary strategies to harness their full potential. As the field evolves, SDE-based therapies stand poised to redefine cancer treatment, transforming the TIME from a fortress of immune evasion into a battleground for tumor eradication.

Keywords

Stem cells; exosomes; cancer; immunomodulation; microRNA; non-coding RNA; lncRNA

1. Introduction

Exosomes are nanosized extracellular vesicles, typically 30-150 nm, released by various cell types into the extracellular space and play crucial roles in intercellular communication. They are formed by invagination of endosomal membranes, leading to the formation of multivesicular bodies (MVBs), which subsequently fuse with the plasma membrane to release exosomes into the extracellular milieu [1, 2]. These vesicles encapsulate a variety of bioactive molecules, including proteins, lipids, and nucleic acids, which contribute to their functionality in mediating cellular communication processes such as immune responses, angiogenesis, and tumor development [1, 3]. The protein composition of exosomes typically induces tetraspanins, heat shock proteins, and various cargo proteins, which can influence recipient cells through receptor-mediated mechanisms or by directly transferring their molecular cargo into the cytoplasm, thereby activating diverse intracellular signaling pathways [2, 4]. Exosomes also contain various types of nucleic acids, including messenger RNAs (mRNAs) and non-coding RNAs (ncRNAs), which have garnered significant interest due to their roles in gene regulation and their potential implications in disease processes, including cancer [5, 6]. By transferring these genetic materials, exosomes can modulate the recipient cell's phenotype and function, acting as vectors for horizontal gene transfer within the tumor microenvironment (TME) and influencing immune responses [7]. This intercellular communication mediated by exosomes is critical for maintaining homeostasis and regulating pathological conditions, including malignancies [3, 8].

Stem cell-derived exosomes (SDEs) exhibit unique properties that distinguish them from exosomes derived from other cell types, notably their immunomodulatory and regenerative

capabilities, as well as their lower immunogenicity [9, 10]. The immunomodulatory properties of SDEs stem from their ability to influence immune cell activation and function, promoting a pro-regenerative environment while simultaneously modulating the TME to favor anti-tumor immunity [11, 12]. Additionally, SDEs demonstrate exceptional regenerative properties that may enhance tissue repair and regeneration following injury, making them valuable therapeutic candidates for various diseases, including cancer [10]. Compared with exosomes from normal cells, those from cancer cells often promote tumorigenesis and immune evasion. Cancer cell-derived exosomes typically carry oncogenic factors, including specific miRNAs and proteins that facilitate tumor growth, metastasis, and immune suppression [13, 14]. For instance, exosomes from triple-negative breast cancer cells can inhibit CD8⁺ T cell functions, thus facilitating immune escape [13, 15]. This highlights a fundamental contrast between SDEs and cancer cell-derived exosomes, emphasizing the potential of SDEs to reprogram the tumor immune microenvironment towards an anti-tumorigenic state [9, 12].

In this review, we focus on stem cell-derived exosomes as active regulators of tumor immune microenvironment (TIME) reprogramming. All discussed topics, including ncRNA cargo selection, immune cell modulation, stromal remodeling, chemoresistance, and exosome engineering, are framed in terms of their contributions to shifting the TIME from an immunosuppressive to an immune-permissive state. This framework emphasizes SDE-associated ncRNAs as system-level modulators of tumor-immune interactions rather than as isolated molecular signals.

2. Non-Coding RNAs in Tumor Microenvironment

ncRNAs, including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), represent a significant class of biomolecules found within exosomes. These ncRNAs play vital roles in regulating gene expression and cellular processes, making them critical components of exosomal cargo in modulating the TME [4, 5]. miRNAs, small regulatory RNAs approximately 20-24 nucleotides in length, can silence target genes post-transcriptionally, influencing various cellular phenotypes, including immune cell differentiation, activation, and apoptosis [6, 7]. lncRNAs and circRNAs can modulate gene expression at both transcriptional and post-transcriptional levels, and they are essential for cellular signaling and programming [16]. Importantly, ncRNAs carried by exosomes are increasingly recognized as key mediators of TME modulation. They can influence immune cell responses, alter chemokine and cytokine gradients, and contribute to immune escape mechanisms [7, 17]. For instance, exosomal miRNAs may downregulate immune checkpoint molecules such as programmed death-ligand 1 (PD-L1) in tumor-associated immune cells, thereby enhancing anti-tumor immunity [4, 17]. The notion that ncRNAs within exosomes can reshape the TME underscores their potential as therapeutic agents for reprogramming tumor immune dynamics [18, 19].

The TIME encompasses a complex network of immune cells, cytokines, stromal components, and tumor cells that collectively shape tumor progression and treatment responses. Critical cellular components of TIME include T lymphocytes (both cytotoxic CD8⁺ cells and regulatory T cells), macrophages, dendritic cells (DCs), and various stromal cells such as cancer-associated fibroblasts (CAFs) [20, 21]. Cytokines and chemokines secreted by these cells orchestrate the immune profile within the TME, influencing whether the immune response is anti-tumorigenic or tumor-promoting [22, 23]. Understanding the role of TIME is essential, as it directly impacts

cancer progression, metastasis, and therapy resistance. Immunosuppressive factors present within the TIME, such as tumor-derived exosomes carrying inhibitory ligands, can effectively hinder T cell activation and cytotoxicity, facilitating tumor immune escape [14, 24]. Additionally, the interplay between immune cells and their microenvironment often determines therapeutic efficacy; immunotherapies may succeed in some tumors while failing in others due to the inherent characteristics of the TIME [5, 21]. As such, unraveling the complexities of the TIME is paramount for developing effective therapeutic strategies aimed at reprogramming immune responses against tumors [10, 22].

Given the transformative potential of stem cell-derived exosomal ncRNAs in mediating immune responses, there is a compelling rationale for investigating their role in reprogramming the TIME. SDEs not only possess inherent immunomodulatory properties but also convey multi-faceted gene regulatory functions through their cargo of ncRNAs, offering a novel strategy to alter the immunosuppressive milieu of tumors. By leveraging the unique immunomodulatory and regenerative properties of stem cell-derived exosomes, researchers can explore whether these exosomal ncRNAs can reshape the TIME to favor anti-tumor immunity, thereby enhancing therapeutic outcomes for cancer patients [4, 12].

3. Stem Cell-Derived Exosomes: Biogenesis and Mechanism of Action

3.1 Biogenesis of Stem Cell-Derived Exosomes

The biogenesis of SDEs involves tightly regulated molecular pathways that orchestrate vesicle formation, cargo sorting, and secretion. The process initiates with the invagination of the endosomal membrane, forming intraluminal vesicles (ILVs) within MVBs. This process is regulated by ESCRT-dependent and ESCRT-independent mechanisms that collectively govern intraluminal vesicle formation and cargo sorting, as extensively reviewed elsewhere [25, 26]. In parallel, ESCRT-independent pathways involving tetraspanins and ceramide-enriched lipid microdomains also contribute to ILV biogenesis and influence cargo selection [25, 27].

Following ILV formation, MVBs either undergo lysosomal degradation or fuse with the plasma membrane via Rab GTPases and SNARE proteins, leading to exosome release. The selective packaging of ncRNAs (e.g., miRNAs, lncRNAs) into ILVs occurs during invagination and is governed by sequence-specific RNA-binding proteins. For instance, hnRNPA2B1 recognizes the GGAG/UGCA motif in miRNAs (e.g., miR-155, miR-21) and undergoes sumoylation, facilitating their loading into exosomes. Similarly, YBX1 binds to lncRNAs (e.g., MALAT1) via cold-shock domains, thereby enriching them in SDEs. Additionally, post-transcriptional modifications, such as 3'-uridylation of miRNAs, serve as sorting signals, directing them to exosomes rather than the cytosol [15, 22]. Notably, unlike cancer-derived exosomes, stem cell-specific features, such as lower nSMase2 activity, favor the selective enrichment of immunomodulatory ncRNAs rather than oncogenic cargo, highlighting the distinct therapeutic potential of stem cell-derived exosomes [28, 29]. These mechanisms provide a framework for engineering SDEs with tailored ncRNA profiles for therapeutic applications (Figure 1) [10, 22].

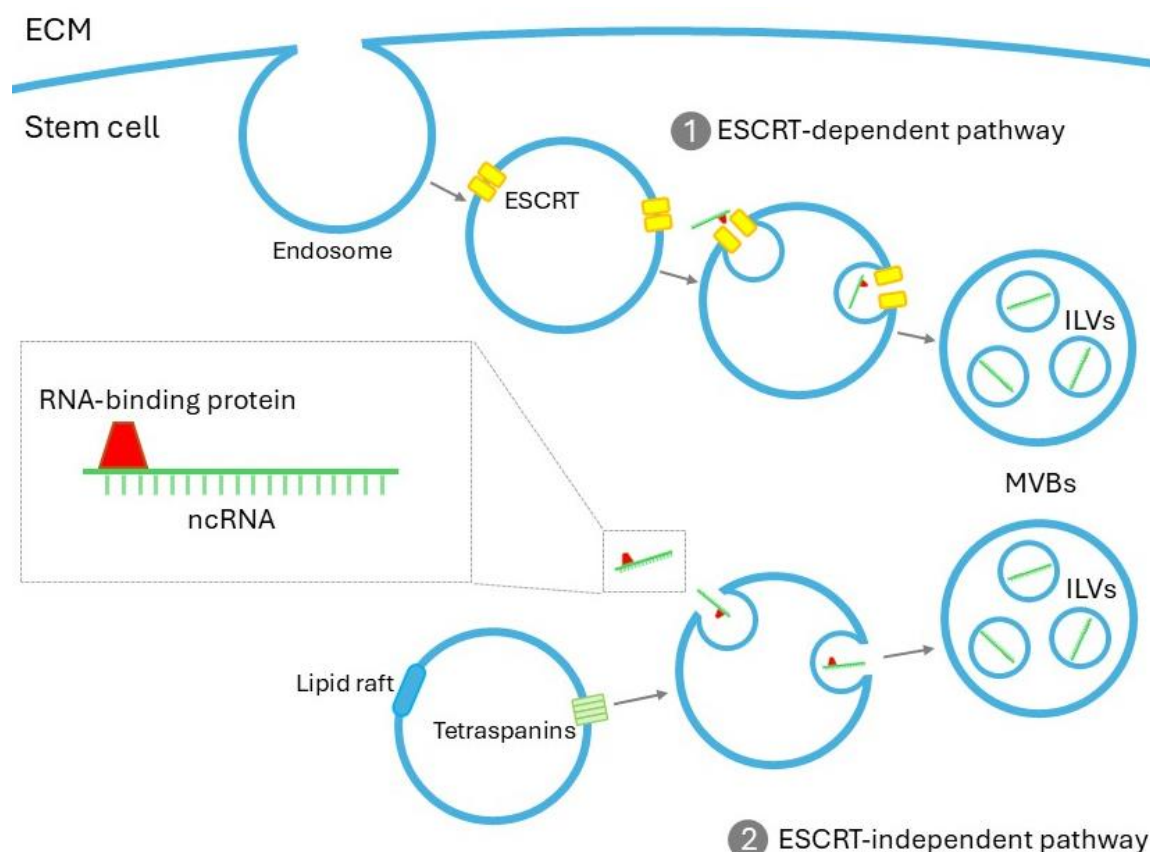


Figure 1 Schematic representation of stem cell-derived exosome biogenesis. Exosomes are generated through ESCRT-dependent and -independent pathways, enabling selective loading and release of ncRNAs into the tumor microenvironment.

3.2 Key ncRNA Cargos in Stem Cell Exosomes

Several ncRNAs carried by SDEs play pivotal roles in immune regulation and tumor biology. Representative examples, including miR-21, miR-34a, and lncRNA MALAT1, modulate immune cell dynamics, immune checkpoint signaling, tumor progression, and therapy response, highlighting the context-dependent immunomodulatory and oncogenic functions of exosomal ncRNAs [4, 7, 30-32].

Emerging evidence underscores the tumor-suppressive potential of exosomal miRNAs. For instance, miR-342-3p, enriched in mesenchymal stem cell-derived exosomes (MSCs-exo), has been shown to inhibit breast cancer metastasis and chemoresistance by targeting Inhibitor of Differentiation 4 (*ID4*). Downregulation of miR-342-3p in metastatic breast cancer tissues correlates with enhanced invasive behavior, while its restoration suppresses these effects, positioning it as a therapeutic candidate for attenuating aggressive tumor phenotypes [33]. Similarly, lncRNA XIST, transmitted via bone marrow MSC-derived exosomes, promotes osteosarcoma progression by sponging miR-655, thereby upregulating ATP-citrate lyase (*ACLY*). This interaction drives lipid deposition and activates β -catenin signaling, fueling tumor growth and lung metastasis. These findings illustrate how SDEs can either restrain or exacerbate malignancy depending on their ncRNA cargo, emphasizing the need for precise therapeutic targeting [34].

The role of SDEs in chemoresistance is exemplified by miR-21-5p, which is enriched in exosomes from doxorubicin-treated MSCs and transferred to breast cancer cells, where it induces

S100A6 expression and drug resistance. Silencing miR-21-5p in MSCs reverses this effect, highlighting its potential as a therapeutic target [35]. Intriguingly, exosomal miR-126 demonstrates a dual role in malignant pleural mesothelioma (MPM). While initially enhancing cancer stem cell (CSC) stemness, prolonged miR-126 accumulation, induced by GW4869, an inhibitor of exosome release, triggers metabolic stress, autophagy dysregulation, and necroptosis, ultimately suppressing tumor growth. Mechanistically, this functional switch has been attributed to sustained metabolic stress and disruption of autophagic flux, leading to increased oxidative stress and activation of necroptotic pathways, including RIPK1/RIPK3 signaling, in cancer stem cells. This paradoxical effect underscores the context-dependent nature of exosomal ncRNAs and the therapeutic potential of modulating exosome trafficking to exploit CSC vulnerabilities [36].

Gastric cancer-derived exosomes impaired adipogenesis in cancer-associated cachexia (CAC) by suppressing lipid droplet formation and promoting brown adipose differentiation in adipose MSCs via exosomal miR-155. Mechanistically, miR-155 targeted C/EBP β , downregulating adipogenic markers (C/EBP α , PPAR γ) and upregulating thermogenic UCP1, shifting adipose MSCs toward energy-expending brown adipose-like cells. In vivo, miR-155-enriched Gastric cancer exosomes exacerbated fat loss and CAC, while miR-155 depletion reversed these effects, confirming its pivotal role in driving adipose remodeling in cachexia [37]. Also, exosomal transfer of miR-155 from cisplatin-resistant (cisRes) to cisplatin-sensitive (cisSens) oral squamous cell carcinoma (OSCC) cells drives chemoresistance by inducing epithelial-to-mesenchymal transition (EMT) and enhancing migratory potential. miR-155 mimics or cisRes-derived exosomes similarly conferred resistance and aggressive traits in cisSens cells, mirroring the phenotypic changes observed in resistant cells. These findings establish exosome-mediated miR-155 shuttling as a key mechanism in cisplatin resistance, offering a therapeutic target to counteract chemoresistance in OSCC [38].

CAFs in urothelial bladder cancer (UBC) promote stemness and chemoresistance via exosomal miR-146a-5p, which upregulates *SVEP1* in CAFs by recruiting *YY1* and targets *ARID1A/PRKAA2* in UBC cells. This dual action inhibits *SOCS1* (activating STAT3) and AMPK α 2 (activating mTOR), driving CSC maintenance and resistance to gemcitabine/cisplatin. Elevated serum exosomal miR-146a-5p levels correlate with advanced tumor stage and relapse risk, positioning it as a biomarker and therapeutic target to disrupt TME-driven chemoresistance in UBC [39].

In another study, genetically modified dental pulp mesenchymal stem cells (DPSCs) secreted exosomes enriched with tumor-suppressive miR-34a, which effectively inhibited breast cancer cell proliferation, migration, and invasion by inducing apoptosis, outperforming liposomes in miRNA delivery efficiency [40]. A summary of key stem cell-derived exosomal ncRNAs, their gene targets, and specific functional roles in cancer is presented in Table 1.

Table 1 Stem cell-derived exosomes carrying ncRNAs involved in cancer.

ncRNA Name	Type	Targeting Gene(s)	Specific Roles	
miR-342-3p	miRNA	<i>ID4</i>	Inhibits breast cancer metastasis and chemoresistance by directly targeting <i>ID4</i> , a transcription factor involved in tumor invasion. Downregulation of miR-342-3p in metastatic tumors correlates with aggressive phenotypes; restoration via mesenchymal stem cell (MSC)-derived exosomes suppresses metastasis and enhances chemotherapy sensitivity.	[33]
lncRNA XIST	lncRNA	miR-655/ <i>ACLY</i>	Sponges miR-655 to upregulate <i>ACLY</i> , driving lipid deposition, β -catenin activation, and osteosarcoma progression via bone marrow MSC-derived exosomes.	[34]
miR-21-5p	miRNA	<i>S100A6</i>	Transferred from doxorubicin-treated MSC exosomes to breast cancer cells, induces chemoresistance via <i>S100A6</i> upregulation. Silencing restores drug efficacy.	[35]
miR-155	miRNA	PD-L1, <i>IRAK1</i> , C/EBP β	Enhances CD8 ⁺ T cell activation. In chemoresistant oral squamous cell carcinoma, it drives epithelial-mesenchymal transition and cisplatin resistance via exosomal transfer.	[38, 41]
miR-223	miRNA	<i>PTEN</i>	Reprograms tumor-associated macrophages from M2 to M1 phenotype, suppresses <i>PTEN</i> , and activates PI3K/AKT in ovarian cancer, driving chemoresistance. Biomarker for recurrence.	[42]
miR-146a-5p	miRNA	<i>SVEP1</i> , <i>ARID1A/PRKAA2</i>	Cancer-associated fibroblasts-derived exosomal miR-146a-5p promotes bladder cancer stemness and chemoresistance via STAT3/mTOR activation. Serum levels correlate with relapse.	[39]
miR-126	miRNA	Not specified	Enhances cancer stem cells' stemness in malignant pleural mesothelioma initially; prolonged accumulation triggers metabolic stress and necroptosis, suppressing tumor growth.	[36]
MALAT1	lncRNA	PD-L1 (indirect)	Upregulates PD-L1 expression via <i>METTL3</i> -mediated m6A modification in pancreatic cancer, thereby increasing T-cell exhaustion and immune evasion.	[32]
miR-34a	miRNA	<i>Notch1</i> (indirect)	Induces apoptosis in breast cancer cells, inhibits proliferation/migration, and outperforms liposomes in delivery efficiency via dental pulp mesenchymal stem cell-derived exosomes.	[40]
miR-21	miRNA	<i>PTEN</i> (implied)	In immune cells, it activates AKT via <i>PTEN</i> suppression; in tumor cells, it promotes chemoresistance via anti-apoptotic pathways.	[43, 44]

3.3 Uptake by Tumor and Immune Cells

The uptake of exosomes by tumor and immune cells involves diverse molecular mechanisms that dictate cargo delivery and functional outcomes. Tumor cells predominantly internalize exosomes via receptor-mediated endocytosis, where surface receptors such as integrins and tetraspanins bind exosomal ligands or phosphatidylserine [45, 46]. This interaction triggers clathrin- or caveolin-dependent endocytosis, enabling exosomes to deliver ncRNA cargos directly into the cytoplasm. These ncRNAs can reprogram tumor cell behavior by modulating tumor suppressive or oncogenic signaling pathways, thereby driving chemoresistance or metastasis [5, 23].

Immune cells exhibit cell-type-specific uptake mechanisms. For example, macrophages internalize exosomes via scavenger or phosphatidylserine-recognizing receptors, which can promote polarization toward pro-inflammatory M1 phenotypes through NF- κ B activation [5, 17]. Dendritic cells capture exosomes through lectin-dependent pathways, enhancing antigen cross-presentation and T cell priming via MHC class II upregulation [47].

Recent advances in exosome engineering exploit these pathways to improve targeting specificity. For instance, exosomes modified with immune receptor-targeting ligands can selectively bind to T cells, enhancing their activation against tumors [46, 48]. Additionally, surface conjugation of pH-sensitive fusogenic elements promotes membrane fusion in acidic tumor microenvironments, ensuring precise cargo release into recipient cells [49, 50]. These mechanisms illustrate how tumor and immune cells process exosomal cargo differently, thereby shaping the tumor immune landscape. Understanding these pathways may facilitate the development of exosome-based strategies to modulate immune responses or tumor behavior (Figure 2) [45, 51]. Collectively, these biogenesis and uptake mechanisms determine how stem cell-derived exosomal ncRNAs are delivered to immune and stromal cells, thereby shaping their capacity to reprogram the TIME.

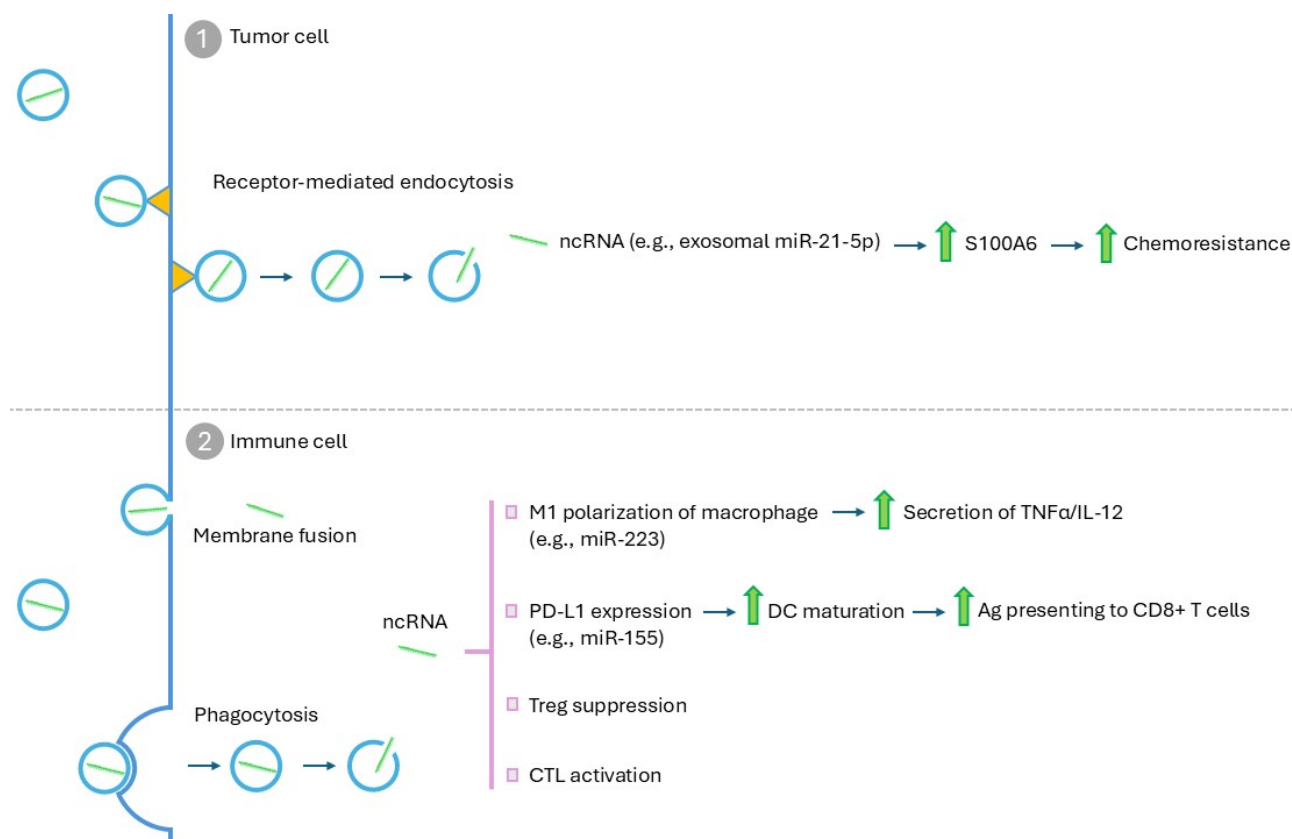


Figure 2 Exosome internalization by tumor and immune cells. Uptake of stem cell-derived exosomes by tumor and immune cells, resulting in differential ncRNA-mediated effects on tumor behavior and anti-tumor immune activation.

4. Reprogramming the Tumor Immune Microenvironment

SDEs reprogram the tumor immune microenvironment through coordinated effects on immune cells, immunosuppressive signaling pathways, and stromal components. SDE-associated ncRNAs act on multiple components of the TIME, collectively promoting a shift toward an immune-permissive state.

4.1 Modulation of Immune Cells

Stem cell-derived exosomes have been shown to play critical roles in modulating various immune cell populations within the TIME.

4.1.1 T-Cells Modulation

One of the key roles of stem cell-derived exosomes is their capacity to enhance the activation and proliferation of cytotoxic CD8⁺ T cells while simultaneously suppressing regulatory T cells (Tregs). As discussed above, several stem cell-derived exosome-associated ncRNAs exert direct immunomodulatory effects on T cell function. For instance, the delivery of exosomal miR-155 has been implicated in promoting T cell activation and augmenting their cytotoxic potential against tumor cells [52, 53]. Conversely, exosomes derived from tumors often carry immunosuppressive factors that downregulate the activity of effector T cells, facilitating immune evasion [15, 54]. This

dual mechanism underlines the potential of utilizing SDEs enriched in specific ncRNAs to generate robust anti-tumor immune responses while thwarting Treg-mediated suppression [3, 17]. Furthermore, elevated reactive oxygen species (ROS) in ovarian cancer cells reduce exosomal miR-155-5p levels; however, neutralization of ROS with N-acetyl-L-cysteine (NAC) restores miR-155-5p levels in tumor exosomes, suppressing macrophage migration and tumor infiltration by targeting PD-L1, thereby enhancing CD8⁺ T cell activity and reducing T cell apoptosis. In vivo, NAC-derived exosomes or direct delivery of exosomal miR-155-5p inhibited ovarian cancer progression, reduced macrophage infiltration, and activated antitumor CD8⁺ T cells more effectively than PD-L1 blockade, suggesting miR-155-5p targets additional immunosuppressive pathways beyond PD-L1. These findings reveal ROS-driven downregulation of miR-155-5p as a key mechanism of immune evasion, proposing exosomal miR-155-5p restoration is a potent strategy to reprogram the immunosuppressive TME [41].

BMSC-derived exosomes alleviate Th17/Treg imbalance by transferring miR-146a-5p to CD4⁺ T cells, which suppresses *IRAK1* expression, reducing pro-inflammatory Th17 cells and promoting regulatory Tregs. Silencing exosomal miR-146a-5p reversed this effect, increasing Th17/Treg ratios, while *IRAK1* overexpression similarly disrupted balance, both counteracted by BMSC exosomal miR-146a-5p. These findings highlight exosomal miR-146a-5p as a therapeutic target for ITP, offering a novel strategy to restore immune homeostasis by inhibiting *IRAK1* [55].

4.1.2 Macrophages

Exosomes derived from stem cells can also polarize macrophages from an M2 (pro-tumor) phenotype towards an M1 (anti-tumor) phenotype. Consistent with the ncRNA cargo profiles described earlier, stem cell-derived exosomes profoundly influence macrophage polarization within the tumor immune microenvironment. For example, exosomal miR-223 has been shown to induce M1 polarization, leading to enhanced secretion of pro-inflammatory cytokines and improved antigen-presenting capabilities, thus promoting anti-tumor immunity [24, 56]. In contrast, tumor-derived exosomes tend to skew macrophage polarization towards an M2 phenotype, fostering an environment conducive to tumor growth and metastasis [5, 57]. Hence, leveraging SDEs to reshape macrophage polarization could be an effective strategy for reprogramming the TME to favor anti-tumor responses. Furthermore, hypoxic epithelial ovarian cancer (EOC) cells recruit macrophages and polarize them into TAM, which secrete exosomes enriched with miR-223 under hypoxia. These exosomes transfer miR-223 to EOC cells, suppressing *PTEN* and activating the PI3K/AKT pathway, thereby driving multidrug resistance in vitro and in vivo. Clinically, elevated HIF-1 α expression correlates with increased CD163⁺ TAM infiltration and intratumoral miR-223 levels, while circulating exosomal miR-223 serves as a biomarker for EOC recurrence, highlighting its therapeutic potential to overcome chemoresistance [42].

4.1.3 Dendritic Cells

Exosomal ncRNAs can enhance DC maturation and antigen-presenting capabilities, which are pivotal for initiating T cell-mediated immune responses. Through the delivery of immunoactive miRNAs, SDEs may facilitate DC activation, thus improving their ability to process and present tumor antigens to T cells, potentially leading to enhanced anti-tumor immunity [26, 56]. This

interaction highlights the importance of exosomal cargo in orchestrating immune responses within the TME.

4.2 Suppression of Immunosuppressive Factors

Utilizing stem cell-derived exosomal miRNAs to downregulate immunosuppressive factors in the TME represents another promising therapeutic strategy. Exosomal exposure can downregulate inhibitory proteins, such as PD-L1, TGF- β , and IL-10, which are often upregulated in the TME to counteract immune responses [3, 4]. For instance, research has indicated that specific miRNAs can inhibit PD-L1 expression in immune cells, thereby attenuating their immunosuppressive effects and restoring T cell functionality [14, 58]. This ability to suppress immunosuppressive signaling pathways could enhance the overall efficacy of cancer immunotherapies. Furthermore, exosomes released by immune cells can interfere with the activities of myeloid-derived suppressor cells (MDSCs), which promote immune tolerance and suppress anti-tumor immunity [57]. The capacity of SDEs to modulate MDSC function by delivering bioactive molecules presents a unique approach to counteracting the immunosuppressive nature of the TME.

4.3 Remodeling the Stromal Niche

Exosomal ncRNAs can also target CAFs and the extracellular matrix (ECM), promoting alterations in the stromal niche that favor anti-tumor immune responses. By delivering specific signaling molecules, SDEs can reprogram CAFs from a tumor-promoting to a tumor-restraining phenotype, thereby reducing extracellular matrix stiffness and enhancing T cell infiltration [48, 53]. This remodeling of the TME not only enhances immune cell access but also alters the chemical signaling environment, potentially increasing therapeutic efficacy against tumors. Moreover, modulation of ECM components by SDEs can help prevent metastasis and promote apoptosis in tumor cells, thereby enhancing the overall anti-tumor efficacy of therapeutic approaches [23, 59]. The interplay between stem cell-derived exosomes and stromal cells underscores the multifaceted role these vesicles play in transforming the TME to support effective immune responses against tumors (Figure 3).

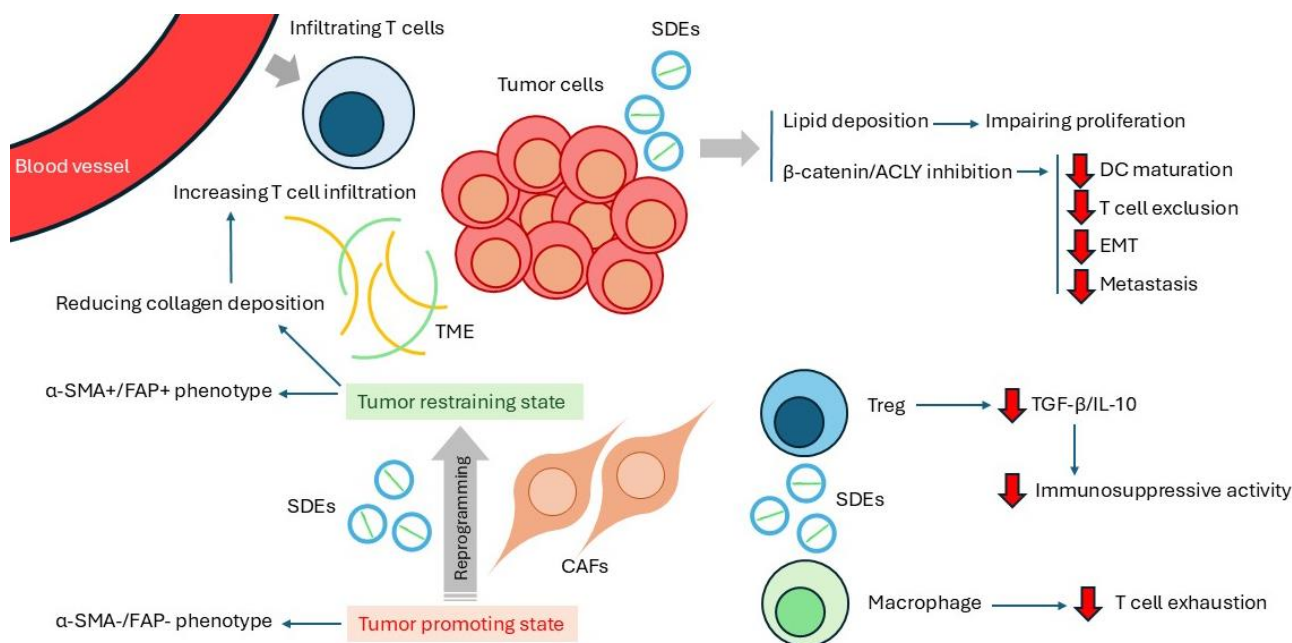


Figure 3 Exosomal ncRNAs remodel the stromal niche. SDEs reprogram CAFs, reduce ECM stiffness, and modulate immunosuppressive pathways, thereby promoting an anti-tumor microenvironment with increased T cell infiltration.

5. Therapeutic Implications

The therapeutic relevance of stem cell-derived exosomes lies in their ability to reprogram the TME rather than directly targeting tumor cells alone. Preclinical studies have established the potential of stem cell-derived exosomes to induce tumor regression, enhance immune infiltration, and confer survival benefits. For instance, exosomes derived from MSCs have been demonstrated to carry anti-tumor miRNAs such as miR-146a that effectively suppress breast cancer metastasis [56]. *In vivo* studies indicate that administration of MSC-derived exosomes leads to considerable tumor shrinkage and increased activation of anti-tumor immune cells, highlighting their potential as therapeutic agents [11, 27]. Additionally, animal models have shown that SDEs can facilitate the recruitment of cytotoxic T cells to the tumor site, thereby improving survival rates in cancer-bearing subjects [4, 31]. These findings collectively underscore the promising role of stem cell-derived exosomes as natural nanoparticles in cancer therapy.

Despite the promising preclinical findings, several challenges hinder the clinical translation of stem cell-derived exosomes. Scalability in the production of these exosomes remains a significant barrier, as efficient protocols for large-scale isolation and purification have yet to be standardized [23, 27]. Furthermore, ensuring the safety of exosome-based therapies is paramount, as concerns regarding off-target effects and potential immunogenicity must be rigorously evaluated [60, 61]. Furthermore, targeting specificity is another critical challenge, as tumor heterogeneity and microenvironmental variability complicate the predictability of therapeutic effects [14, 59]. Therefore, addressing these clinical translation challenges will be essential to the successful development of exosome-based therapies for cancer treatment.

Combining stem cell-derived exosomes with existing therapies, such as immune checkpoint inhibitors or chemotherapy, holds significant potential to enhance therapeutic efficacy. For example, co-administration of SDEs enriched with immunomodulatory miRNAs alongside anti-PD-

1 or anti-PD-L1 therapies may synergistically reinvigorate exhausted T cells within the TIME, resulting in improved immune responses against tumors [3, 62, 63]. This combinatorial approach leverages both adaptive and innate immune mechanisms, potentially maximizing therapeutic outcomes while minimizing adverse effects.

6. Challenges and Future Directions

The field of exosome research continues to grapple with critical technical and biological challenges. A significant bottleneck lies in the isolation and characterization of exosomes, which remain hampered by their heterogeneity in size, density, and molecular composition. Current techniques, such as ultracentrifugation and size-exclusion chromatography, often co-isolate non-exosomal contaminants, such as apoptotic bodies and lipoproteins, skewing downstream analyses [64, 65]. Moreover, variability in exosomal surface markers, such as tetraspanins (CD9, CD63, CD81) and adhesion molecules (ICAM-1, MFGE8), across cell types and tumor subtypes complicates standardized purification protocols. For instance, exosomes from MSCs exhibit distinct lipidomic profiles (e.g., higher ceramide content) compared to those from induced pluripotent stem cells (iPSCs), influencing their functional properties [66, 67].

Another barrier is the lack of large-scale clinical trials validating exosome-based therapies (21). For example, miR-21-5p in SDEs may inadvertently activate oncogenic pathways in healthy tissues if not selectively targeted. Additionally, the impact of tumor-specific mutations on exosomal ncRNA function remains underexplored. Mutations in *TP53* or *KRAS* could alter the binding affinity of exosomal miRNAs (e.g., miR-34a) to their target mRNAs, diminishing therapeutic efficacy in genetically diverse tumors [46].

Unanswered questions persist regarding the optimal stem cell source for exosome production. iPSC-derived exosomes, enriched in pluripotency-associated miRNAs (e.g., miR-302), may enhance regenerative properties but risk teratoma formation, whereas MSC-derived exosomes offer safer profiles but vary in potency depending on tissue origin [14]. Similarly, the role of epigenetic modifications (e.g., DNA methylation, histone acetylation) in regulating exosomal ncRNA cargo remains unclear, presenting opportunities for mechanistic exploration. Future efforts should prioritize engineering exosomes to overcome these limitations. Surface modifications, such as conjugating exosomes with EGFR-targeting nanobodies or CXCR4-binding peptides, could enhance tumor homing. CRISPR/Cas9-edited exosomes, loaded with tumor-suppressive miRNAs (e.g., miR-34a) and immune-activating lncRNAs (e.g., NKILA), offer precision in reprogramming the TIME. Furthermore, personalized ncRNA cocktails, tailored to a patient's tumor mutational burden or immune profile, could synergize with existing therapies. For example, combining exosomal miR-155 (to activate CD8⁺ T cells) and anti-PD-1 antibodies might overcome resistance in *TP53*-mutant cancers [48, 68].

7. Conclusion

In conclusion, stem cell-derived exosomal ncRNAs represent a novel, versatile, and biocompatible strategy for reprogramming the tumor immune microenvironment. Rather than acting through isolated molecular interactions, SDE-associated ncRNAs exert coordinated, system-level effects on immune cells, immunosuppressive signaling pathways, and stromal components. Together, these effects shift the TIME from an immunosuppressive toward an immune-permissive

state. This unifying framework integrates ncRNA cargo delivery, exosome biogenesis and uptake, immune modulation, stromal remodeling, and mechanisms of therapy resistance into a coherent model of TIME reprogramming. From a translational perspective, these properties position SDEs as promising candidates for the development of next-generation cancer immunomodulatory therapies. Nevertheless, several challenges must be addressed before clinical implementation, including scalable, standardized exosome production, addressing cargo heterogeneity, ensuring targeting specificity, and assessing long-term safety. Recent advances in exosome engineering, such as surface modification for enhanced tumor targeting, controlled ncRNA-loading strategies, and CRISPR-based exosome editing, may help overcome these limitations. Furthermore, combining SDE-based approaches with immune checkpoint inhibitors or developing personalized, tumor-specific ncRNA cocktail strategies holds considerable promise for enhancing therapeutic efficacy. Collectively, these advances highlight the potential of stem cell-derived exosomal ncRNAs to bridge mechanistic insights with translational innovation in precision oncology.

Acknowledgments

Acknowledge the people or organization(s) that have technically supported this work, excluding fund provider.

Author Contributions

Manal Hadi Ghaffoori Kanaan: conceptualization, supervision, writing – original draft, writing – review & editing; Beom-Jin Lee: conceptualization, investigation, writing – review & editing; Sura Saad Abdullah: writing – original draft, investigation; Chulhun Park: writing – review & editing; Abdolmajid Ghasemian: writing – review & editing; Steward Mudenda: writing – review & editing. All the authors critically revised and approved the final version of the manuscript.

Competing Interests

The authors declare no competing interests related to this research.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

AI-Assisted Technologies Statement

ChatGPT4o and DeepSeekR1 were used for language editing, grammatical checks, and text refinement. Authors approved all sections of the article and accept the correspondence of all contents.

References

1. Xu Z, Zeng S, Gong Z, Yan Y. Exosome-based immunotherapy: A promising approach for cancer treatment. *Mol Cancer*. 2020; 19: 160.
2. Liu Y, Shi K, Chen Y, Wu X, Chen Z, Cao K, et al. Exosomes and their role in cancer progression. *Front Oncol*. 2021; 11: 639159.
3. Liu J, Ren L, Li S, Li W, Zheng X, Yang Y, et al. The biology, function, and applications of exosomes in cancer. *Acta Pharm Sin B*. 2021; 11: 2783-2797.
4. Matsuzaka Y, Yashiro R. Immune modulation using extracellular vesicles encapsulated with MicroRNAs as novel drug delivery systems. *Int J Mol Sci*. 2022; 23: 5658.
5. Li Q, Wang H, Peng H, Huyan T, Cacalano NA. Exosomes: Versatile nano mediators of immune regulation. *Cancers*. 2019; 11: 1557.
6. Wu B, Wang Q, Shi X, Jiang M. Targeting endocytosis and cell communications in the tumor immune microenvironment. *Cell Commun Signal*. 2022; 20: 161.
7. Tickner JA, Urquhart AJ, Stephenson SA, Richard DJ, O'Byrne KJ. Functions and therapeutic roles of exosomes in cancer. *Front Oncol*. 2014; 4: 127.
8. Fanini F, Fabbri M. Cancer-derived exosomal microRNAs shape the immune system within the tumor microenvironment: State of the art. *Semin Cell Dev Biol*. 2017; 67: 23-28.
9. Qiu H, Liang J, Yang G, Xie Z, Wang Z, Wang L, et al. Application of exosomes in tumor immunity: Recent progresses. *Front Cell Dev Biol*. 2024; 12: 1372847.
10. Lema DA, Burlingham WJ. Role of exosomes in tumour and transplant immune regulation. *Scand J Immunol*. 2019; 90: e12807.
11. Shi K, Fu W, Farhadi Sabet Z, Ye J, Liang S, Liu T, et al. Hydrogel-mediated jamming of exosome communications that counter tumor adaption in the tumor immune microenvironment. *ACS Nano*. 2024; 18: 33042-33057.
12. Zhu X, Ma D, Yang B, An Q, Zhao J, Gao X, et al. Research progress of engineered mesenchymal stem cells and their derived exosomes and their application in autoimmune/inflammatory diseases. *Stem Cell Res Ther*. 2023; 14: 71.
13. Gangadaran P, Madhyastha H, Madhyastha R, Rajendran RL, Nakajima Y, Watanabe N, et al. The emerging role of exosomes in innate immunity, diagnosis and therapy. *Front Immunol*. 2023; 13: 1085057.
14. Zeng QL, Liu DW. Mesenchymal stem cell-derived exosomes: An emerging therapeutic strategy for normal and chronic wound healing. *World J Clin Cases*. 2021; 9: 6218.
15. Li T, Jiao J, Ke H, Ouyang W, Wang L, Pan J, Li X. Role of exosomes in the development of the immune microenvironment in hepatocellular carcinoma. *Front Immunol*. 2023; 14: 1200201.
16. Zhang W, Yan Y, Peng J, Thakur A, Bai N, Yang K, et al. Decoding roles of exosomal lncRNAs in tumor-immune regulation and therapeutic potential. *Cancers*. 2022; 15: 286.
17. Zheng Q, Zhang S, Guo WZ, Li XK. The unique immunomodulatory properties of MSC-derived exosomes in organ transplantation. *Front Immunol*. 2021; 12: 659621.
18. Chen X, Chi H, Zhao X, Pan R, Wei Y, Han Y. Role of exosomes in immune microenvironment of hepatocellular carcinoma. *J Oncol*. 2022; 2022: 2521025.
19. Li J, Zhou W, Wang H, Huang M, Deng H. Exosomal circular RNAs in tumor microenvironment: An emphasis on signaling pathways and clinical opportunities. *MedComm*. 2024; 5: e70019.

20. Yao X, Tu Y, Xu Y, Guo Y, Yao F, Zhang X. Endoplasmic reticulum stress-induced exosomal miR-27a-3p promotes immune escape in breast cancer via regulating PD-L1 expression in macrophages. *J Cell Mol Med*. 2020; 24: 9560-9573.
21. Hazrati A, Soudi S, Malekpour K, Mahmoudi M, Rahimi A, Hashemi SM, et al. Immune cells-derived exosomes function as a double-edged sword: Role in disease progression and their therapeutic applications. *Biomark Res*. 2022; 10: 30.
22. Huang M, Huang X, Huang N. Exosomal circGSE1 promotes immune escape of hepatocellular carcinoma by inducing the expansion of regulatory T cells. *Cancer Sci*. 2022; 113: 1968-1983.
23. Engeroff P, Vogel M. The potential of exosomes in allergy immunotherapy. *Vaccines*. 2022; 10: 133.
24. Zhu T, Kong M, Li C, Shao C. Exosomal miRNAs in the plasma of *Cynoglossus semilaevis* infected with *Vibrio harveyi*: Pleiotropic regulators and potential biomarkers involved in inflammatory and immune responses. *Front Immunol*. 2022; 13: 949670.
25. Ludwig S, Marczak L, Sharma P, Abramowicz A, Gawin M, Widlak P, et al. Proteomes of exosomes from HPV (+) or HPV (-) head and neck cancer cells: Differential enrichment in immunoregulatory proteins. *Oncoimmunology*. 2019; 8: e1593808.
26. Zech D, Rana S, Büchler MW, Zöller M. Tumor-exosomes and leukocyte activation: An ambivalent crosstalk. *Cell Commun Signal*. 2012; 10: 37.
27. Xu F, Luo S, Lu P, Cai C, Li W, Li C. Composition, functions, and applications of exosomal membrane proteins. *Front Immunol*. 2024; 15: 1408415.
28. Sinha D, Roy S, Saha P, Chatterjee N, Bishayee A. Trends in research on exosomes in cancer progression and anticancer therapy. *Cancers*. 2021; 13: 326.
29. Han XQ, Long Y, Yu J. The interaction between tumor derived exosomes and various cells in the progress of tumor. *Highlights Sci Eng Technol*. 2023; 36: 303-311.
30. Tuo B, Chen Z, Dang Q, Chen C, Zhang H, Hu S, et al. Roles of exosomal circRNAs in tumour immunity and cancer progression. *Cell Death Dis*. 2022; 13: 539.
31. Ren B, Li X, Zhang Z, Tai S, Yu S. Exosomes: A significant medium for regulating drug resistance through cargo delivery. *Front Mol Biosci*. 2024; 11: 1379822.
32. Song Z, Wang X, Chen F, Chen Q, Liu W, Yang X, et al. LncRNA MALAT1 regulates METTL3-mediated PD-L1 expression and immune infiltrates in pancreatic cancer. *Front Oncol*. 2022; 12: 1004212.
33. Yu S, Zhou Y, Niu L, Qiao Y, Yan Y. Mesenchymal stem cell-derived exosome mir-342-3p inhibits metastasis and chemo-resistance of breast cancer through regulating ID4. *Genes Genom*. 2022; 44: 539-550.
34. Zhu G, Xia Y, Zhao Z, Li A, Li H, Xiao T. LncRNA XIST from the bone marrow mesenchymal stem cell derived exosome promotes osteosarcoma growth and metastasis through miR-655/ACLY signal. *Cancer Cell Int*. 2022; 22: 330.
35. Luo T, Liu Q, Tan A, Duan L, Jia Y, Nong L, et al. Mesenchymal stem cell-secreted exosome promotes chemoresistance in breast cancer via enhancing miR-21-5p-mediated S100A6 expression. *Mol Ther Oncolytics*. 2020; 19: 283-293.
36. Monaco F, De Conti L, Vodret S, Zanutta N, Comar M, Manzotti S, et al. Force-feeding malignant mesothelioma stem-cell like with exosome-delivered miR-126 induces tumour cell killing. *Transl Oncol*. 2022; 20: 101400.

37. Gao X, Zhou J, Wang J, Dong X, Chang Y, Jin Y. Mechanism of exosomal miR-155 derived from bone marrow mesenchymal stem cells on stemness maintenance and drug resistance in myeloma cells. *J Orthop Surg Res.* 2021; 16: 637.
38. Kirave P, Gondaliya P, Kulkarni B, Rawal R, Garg R, Jain A, et al. Exosome mediated miR-155 delivery confers cisplatin chemoresistance in oral cancer cells via epithelial-mesenchymal transition. *Oncotarget.* 2020; 11: 1157.
39. Zhuang J, Shen L, Li M, Sun J, Hao J, Li J, et al. Cancer-associated fibroblast-derived miR-146a-5p generates a niche that promotes bladder cancer stemness and chemoresistance. *Cancer Res.* 2023; 83: 1611-1627.
40. Vakhshiteh F, Rahmani S, Ostad SN, Madjd Z, Dinarvand R, Atyabi F. Exosomes derived from miR-34a-overexpressing mesenchymal stem cells inhibit in vitro tumor growth: A new approach for drug delivery. *Life Sci.* 2021; 266: 118871.
41. Li X, Wang S, Mu W, Barry J, Han A, Carpenter RL, et al. Reactive oxygen species reprogram macrophages to suppress antitumor immune response through the exosomal miR-155-5p/PD-L1 pathway. *J Exp Clin Cancer Res.* 2022; 41: 41.
42. Zhu X, Shen H, Yin X, Yang M, Wei H, Chen Q, et al. Macrophages derived exosomes deliver miR-223 to epithelial ovarian cancer cells to elicit a chemoresistant phenotype. *J Exp Clin Cancer Res.* 2019; 38: 81.
43. Zheng P, Chen L, Yuan X, Luo Q, Liu Y, Xie G, et al. Exosomal transfer of tumor-associated macrophage-derived miR-21 confers cisplatin resistance in gastric cancer cells. *J Exp Clin Cancer Res.* 2017; 36: 53.
44. He W, Wang C, Mu R, Liang P, Huang Z, Zhang J, et al. MiR-21 is required for anti-tumor immune response in mice: An implication for its bi-directional roles. *Oncogene.* 2017; 36: 4212-4223.
45. Awadasseid A, Wu Y, Zhang W. Extracellular vesicles (exosomes) as immunosuppressive mediating variables in tumor and chronic inflammatory microenvironments. *Cells.* 2021; 10: 2533.
46. Wu T, Liu Y, Ali NM, Zhang B, Cui X. Effects of exosomes on tumor bioregulation and diagnosis. *ACS Omega.* 2023; 8: 5157-5168.
47. Birkholz K, Schwenkert M, Kellner C, Gross S, Fey G, Schuler-Thurner B, et al. Targeting of DEC-205 on human dendritic cells results in efficient MHC class II-restricted antigen presentation. *Blood.* 2010; 116: 2277-2285.
48. Xu J, Chang X, Zhang H, Si M, Su H, Cao L, et al. Exosomes: A bridge of periodontitis and systemic diseases. *Gene Protein Dis.* 2022; 1: 99.
49. Efimova AA, Popov AS, Kazantsev AV, Semenyuk PI, Le-Deygen IM, Lukashev NV, et al. pH-Sensitive Liposomes with Embedded 3-(isobutylamino) cholan-24-oic Acid: What is the possible mechanism of fast cargo release? *Membranes.* 2023; 13: 407.
50. Bebelman MP, Bun P, Huveneers S, van Niel G, Pegtel DM, Verweij FJ. Real-time imaging of multivesicular body-plasma membrane fusion to quantify exosome release from single cells. *Nat Protoc.* 2020; 15: 102-121.
51. Yin T, Xin H, Yu J, Teng F. The role of exosomes in tumour immunity under radiotherapy: Eliciting abscopal effects? *Biomark Res.* 2021; 9: 22.
52. Cao J, Lv G, Wei F. Engineering exosomes to reshape the immune microenvironment in breast cancer: Molecular insights and therapeutic opportunities. *Clin Transl Med.* 2024; 14: e1645.

53. He Y, He Z, Leone S, Liu S. Milk exosomes transfer oligosaccharides into macrophages to modulate immunity and attenuate adherent-invasive *E. coli* (AIEC) infection. *Nutrients*. 2021; 13: 3198.
54. Gong T, Liu YT, Fan J. Exosomal mediators in sepsis and inflammatory organ injury: Unraveling the role of exosomes in intercellular crosstalk and organ dysfunction. *Mil Med Res*. 2024; 11: 24.
55. He Y, Ji D, Lu W, Li F, Huang X, Huang R, et al. Bone marrow mesenchymal stem cell-derived exosomes induce the Th17/Treg imbalance in immune thrombocytopenia through miR-146a-5p/IRAK1 axis. *Hum Cell*. 2021; 34: 1360-1374.
56. Huang J, Su Y. Mechanism and means of exosomes in the treatment of osteoarthritis. *Highlights Sci Eng Technol*. 2023; 36: 836-841.
57. Abudoureyimu M, Zhou H, Zhi Y, Wang T, Feng B, Wang R, et al. Recent progress in the emerging role of exosome in hepatocellular carcinoma. *Cell Prolif*. 2019; 52: e12541.
58. Roy A, As SG, Ganesh PS, Saravanan M, Sunny B. Exosome mediated cancer therapeutic approach: Present status and future prospectives. *Asian Pac J Cancer Prev*. 2023; 24: 363-373.
59. Howitt J, Hill AF. Exosomes in the pathology of neurodegenerative diseases. *J Biol Chem*. 2016; 291: 26589-26597.
60. Guan XL, Guan XY, Zhang ZY. Roles and application of exosomes in the development, diagnosis and treatment of gastric cancer. *World J Gastrointest Oncol*. 2024; 16: 630.
61. Wang X, Huang J, Chen W, Li G, Li Z, Lei J. The updated role of exosomal proteins in the diagnosis, prognosis, and treatment of cancer. *Exp Mol Med*. 2022; 54: 1390-1400.
62. Ivanova E, Asadullina D, Gilyazova G, Rakhimov R, Izmailov A, Pavlov V, et al. Exosomal MicroRNA levels associated with immune checkpoint inhibitor therapy in clear cell renal cell carcinoma. *Biomedicines*. 2023; 11: 801.
63. Zhao C, Cheng L, Li A, Wang H, Li X, Xu J. EGFR-Mutant Lung Adenocarcinoma Cell-Derived Exosomal miR-651-5p Induces CD8+ T Cell Apoptosis via Downregulating BCL2 Expression. *Biomedicines*. 2025; 13: 482.
64. Lai JJ, Chau ZL, Chen SY, Hill JJ, Korpany KV, Liang NW, et al. Exosome processing and characterization approaches for research and technology development. *Adv Sci*. 2022; 9: 2103222.
65. Zhu L, Sun HT, Wang S, Huang SL, Zheng Y, Wang CQ, et al. Isolation and characterization of exosomes for cancer research. *J Hematol Oncol*. 2020; 13: 152.
66. Larios J, Mercier V, Roux A, Gruenberg J. ALIX-and ESCRT-III-dependent sorting of tetraspanins to exosomes. *J Cell Biol*. 2020; 219: e201904113.
67. Shubhra QT, Veranič P, Wang Z. Amplifying antitumor immunity with iPSC-derived exosomes. *Mol Ther*. 2023; 31: 2300-2301.
68. Gong Y, Wei X, Sun W, Ren X, Chen J, Aweya JJ, et al. Exosomal miR-224 contributes to hemolymph microbiota homeostasis during bacterial infection in crustacean. *PLoS Pathog*. 2021; 17: e1009837.