

Review

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Review

The Emerging Role of Exosome-Derived miRNAs in Cancer and Cancer Stem Cells

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Abstract

Exosomes are lipid bilayer vesicles measuring 30–150 nm in diameter that serve as crucial mediators of intercellular communication. By transporting bioactive molecules such as proteins and nucleic acids, they play a pivotal role in cancer progression. Among their cargo, exosomal microRNAs (miRNAs) are central to epigenetic regulation and signal transduction. Cancer stem cells (CSCs), a distinct subpopulation with self-renewal and multi-lineage differentiation capabilities, drive tumor initiation, metastasis, and recurrence, making them critical therapeutic targets. This review systematically summarizes the regulatory mechanisms of exosomal miRNAs in tumorigenesis, metastasis, and drug resistance, with a particular focus on their roles in maintaining CSC properties and promoting therapy resistance. We further discuss their clinical potential as liquid biopsy biomarkers and therapeutic targets. Finally, we outline current research limitations and future directions to advance precision oncology.

Keywords: exosomes; miRNA; cancer; CSCs

1. Introduction

Cancer remains one of the most formidable threats to global public health. According to the latest global cancer burden report (2022), approximately 20 million new cancer cases were diagnosed worldwide, with cancer-related deaths reaching 9.7 million [1]. While significant advancements in cancer therapeutics have improved patient survival rates and quality of life, clinical outcomes continue to be hampered by tumor recurrence, metastasis, and drug resistance [2]. Emerging evidence highlights the pivotal role of CSCs in tumor progression and therapy failure. Characterized by their self-renewal capacity, multilineage differentiation potential, and intrinsic resistance to conventional therapies, CSCs are now recognized as key drivers of tumor initiation, metastatic dissemination, and post-treatment relapse [3]. The dynamic interplay between CSCs and their tumor microenvironment (TME), particularly through intercellular communication, has recently emerged as a critical area of cancer research. Among the mediators of cell-cell crosstalk, exosomes (30–150 nm extracellular vesicles) have gained considerable attention as essential information carriers [4]. These nanoscale vesicles transport bioactive molecules, including miRNAs, which post-transcriptionally regulate gene expression in recipient cells. Notably, exosomal miRNAs have been implicated in various hallmarks of cancer, from tumorigenesis to metastatic colonization [5]. Of particular interest, recent studies reveal that exosome-derived miRNAs participate in sophisticated regulatory networks that govern CSC stemness maintenance, therapy resistance, and metastatic competence [6]. Elucidating the molecular mechanisms by which exosomal miRNAs regulate CSCs and cancer progression holds dual significance: it provides novel insights into tumor heterogeneity and recurrence while offering promising avenues for developing CSC-targeted therapeutic strategies. This research direction may ultimately overcome current clinical challenges in cancer treatment, particularly in addressing therapeutic resistance and preventing metastatic spread.

2. Biogenesis and miRNA Sorting of Exosomes

Exosomes are extracellular vesicles containing various components such as proteins, nucleic acids, and lipids. They are widely present in biological fluids and participate in functions including intercellular information transmission, immune responses, and tissue repair. Additionally, they can serve as carriers for targeted tumor delivery, enhancing therapeutic efficacy. Notably, due to their natural biocompatibility and targeting ability, exosomes have emerged as ideal carriers for novel drug delivery systems, demonstrating significant advantages in targeted tumor therapy [7]. The biogenesis of exosomes is a highly programmed and precisely regulated multi-step process (Figure 1). This process begins with the internalization of the plasma membrane: under clathrin-mediated endocytosis, the plasma membrane invaginates to form early endosomes. Subsequently, under the precise regulation of the endosomal sorting complex required for transport (ESCRT) system, the early endosomal membrane buds inward to form multiple intraluminal vesicles (ILVs), gradually developing into mature multivesicular bodies (MVBs) [8,9]. The ESCRT system, through a cascade reaction of its core components (ESCRT-0 to ESCRT-III) in collaboration with ATPases such as VPS4, accomplishes the selective sorting of cargo molecules (e.g., transmembrane proteins, nucleic acids) and vesicle formation [10–12]. The fate determination of MVBs is a critical regulatory node in exosome generation: on one hand, MVBs can fuse with lysosomes and be degraded by hydrolytic enzymes such as cathepsins, a process regulated by GTPases like Rab7; on the other hand, mediated by GTPases such as Rab27a/b and Rab35, as well as SNARE proteins (e.g., VAMP7, Syntaxin-4), MVBs migrate directionally to the plasma membrane and fuse with it, releasing ILVs into the extracellular space via exocytosis, thereby forming exosomes [13]. The release of exosomes is a tightly regulated process involving the coordinated action of multiple Rab GTPases, SNARE proteins, and cytoskeletal components. This ensures their spatiotemporally precise secretion, enabling exosomes to mediate critical biological functions, including intercellular communication, material transport, and regulatory signaling [14].

The sorting of miRNAs into exosomes is a highly sophisticated and precisely regulated process involving multiple mechanisms: (1) Lipid microdomain-dependent sorting mediated by membrane components like cholesterol and sphingolipids, with nSMase2 playing a key regulatory role as demonstrated by Kosaka et al. [15] and subsequent breast cancer studies [16]; (2) RBP-mediated sorting through specific recognition of miRNA motifs by proteins including hnRNPA2B1 (binding GGAG/GCCU sequences) [17], YBX1 (interacting with cold shock domains) [18,19], and Ago2 (affecting miR-142-3p, miR-150 and miR-451 levels) [20]; and (3) 3'-end modification-dependent sorting evidenced by uridylation patterns in urinary and B-cell exosomal miRNAs [21]. While these mechanisms are known to be cell type- and microenvironment-dependent, current understanding remains incomplete due to technical limitations in exosome isolation and miRNA detection, necessitating future multi-omics approaches to fully elucidate the molecular mechanisms and biological significance of exosomal miRNA.

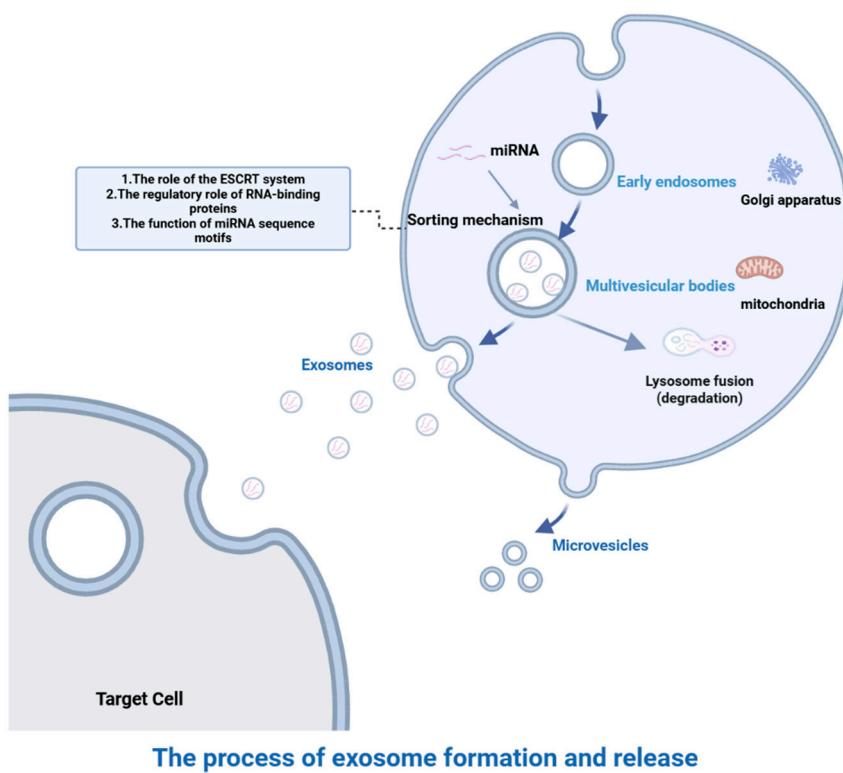


Figure 1. Biogenesis, secretion, and cellular uptake of exosomes. Exosome formation initiates with plasma membrane invagination to generate early endosomes. These compartments mature into late endosomes through additional membrane remodeling, during which they selectively incorporate diverse molecular cargo (including mRNAs, proteins, and lipids) through sophisticated sorting mechanisms. The resulting multivesicular bodies (MVBs) face two distinct fates: (1) lysosomal fusion leading to content degradation, or (2) plasma membrane fusion resulting in exosome secretion.

3. Cancer and Cancer Stem Cells

Cancer stem cells (CSCs) represent a distinct subpopulation within tumor tissues that possess stem cell-like properties including self-renewal capacity, multi-lineage differentiation potential, and tumorigenic ability, thereby being regarded as the "seed cells" responsible for tumor initiation and progression [22]. The seminal discovery in CSC research occurred in 1997 when Bonnet and Dick's research team first successfully identified and isolated leukemia stem cells (LSCs) from acute myeloid leukemia using CD34+/CD38- surface markers, marking a groundbreaking advancement in the field [23]. Subsequent progress in tumor biology has enabled researchers to identify CSC populations in various solid tumors (including breast cancer, glioma, hepatocellular carcinoma, gastric cancer, colorectal cancer, and ovarian cancer) through specific biomarkers such as CD44, CD133, and ALDH1 [24]. Notably, the expression profiles of CSC surface markers exhibit remarkable tumor-type specificity: ALDH+, CD44+, and CD133+ are predominantly expressed in head and neck cancer CSCs [25]; CD200+ and CD166+ are highly expressed in colorectal CSCs [26,27]; while pancreatic CSCs specifically overexpress markers including CD44/CD24 and epithelial-specific antigens [28]. Although CSCs typically constitute only 0.01-2% of the total tumor cell population, they play a pivotal role in tumor initiation, progression, metastasis, and recurrence [29]. Furthermore, CSCs frequently reside in a quiescent state within the cell cycle while overexpressing various drug resistance-associated molecules (such as ABC transporters and DNA damage repair enzymes), thereby serving as crucial mediators of therapeutic resistance. Mare et al. [30] demonstrated that paclitaxel-pretreated MCF7 breast cancer cells exhibited significantly enhanced stem cell properties, as evidenced by increased tumor sphere formation capacity, providing direct evidence for the central role of CSCs in chemoresistance. Recent studies have further revealed that beyond their remarkable self-renewal capacity, CSCs display unique "phenotypic plasticity" -the ability to undergo epithelial-mesenchymal

transition (EMT) or dedifferentiation in response to microenvironmental cues (such as hypoxia and inflammatory cytokines), thereby generating adaptive tumor cell subpopulations. This plasticity not only substantially contributes to tumor heterogeneity but also plays a critical role in metastasis and treatment resistance [31]. At the molecular level, CSCs maintain their stemness and regulate vital biological processes (including survival, proliferation, and differentiation) through aberrant activation of key signaling pathways (such as Wnt/β-catenin, Notch, and PI3K/AKT/mTOR) accompanied by specific epigenetic modifications (including DNA methylation and histone modifications) [32].

4. Role of Exosomal miRNAs in Cancer

Exosomal miRNAs serve as pivotal mediators of intercellular communication in cancer, orchestrating long-distance regulatory effects through their stable circulatory transport system to play essential roles in tumor progression (Figure 2 and Table 1). These molecular regulators exert multifaceted effects by: (1) remodeling the tumor microenvironment through angiogenesis promotion and immunosuppression induction to facilitate immune evasion; (2) activating epithelial-mesenchymal transition (EMT) to enhance metastatic potential; and (3) transmitting drug-resistance genes and reprogramming cellular metabolism to promote tumor cell survival and proliferation.

The progress of exosome-derived miRNAs in tumors

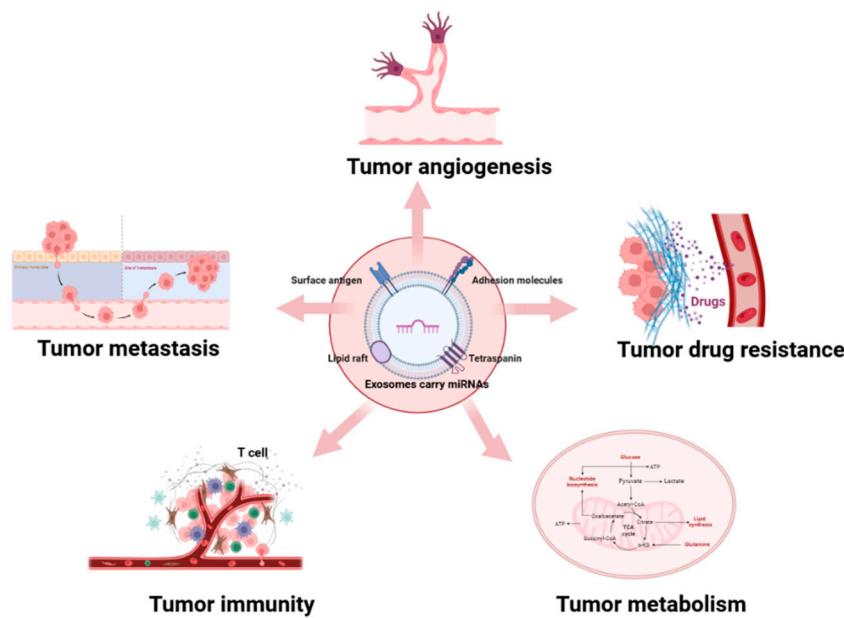


Figure 2. Roles of exosomal miRNAs in tumor progression. Exosomal miRNAs can accelerate tumor metastasis, induce angiogenesis, enhance drug resistance and tumor metabolic reprogramming, and contribute to the formation of a tumor-promoting and immunosuppressive microenvironment.

Table 1. Roles of exosomal miRNAs in cancer progression and cancer stem cell stemness maintenance.

Exosomal miRNA	Source	Function	Mechanism	Reference
miR-200b	Colorectal cancer	Promotes tumor growth	Specifically binds to the 3'-UTR of tumor suppressor p27, reducing its expression	[34]
miR-584	Hepatocellular carcinoma	Promotes tumor growth	Targets TAK1 and related signaling pathways, leading to	[35]

			downregulation of TAK1 expression	
miR-148a	Glioblastoma	Promotes tumor growth	Targets CADM1 to relieve its inhibitory effect on the STAT3 pathway	[36]
miR-1246	Breast cancer	Promotes tumor growth	Specifically downregulates cyclin G2 (CCNG2), disrupting the cell cycle regulatory network	[37]
miR-128	Breast cancer	Promotes tumor metastasis	Regulates the balance of Bcl-2 family proteins (e.g., pro-apoptotic factor Bax), inhibiting initiation of apoptosis	[38]
miR-21	Oral squamous cell carcinoma	Promotes tumor metastasis	Regulates EMT core transcription factor Snail; upregulates vimentin and downregulates E-cadherin expression	[40]
miR-19b-3p	Renal cell carcinoma	Promotes tumor metastasis	Reduces PTEN expression, inducing EMT	[41]
miR-193a-3p, miR-210-3p, miR-5100	Mesenchymal stem cells	Promotes tumor metastasis	Activates STAT3 signaling and induces EMT, promoting lung cancer metastasis	[42]
miR-335-5p	Colorectal cancer	Promotes tumor metastasis	Targets RASA1 to promote EMT	[43]
miR-103	Hepatocellular carcinoma	Promotes tumor angiogenesis	Targets multiple endothelial junction proteins (VE-cadherin, p120-catenin, ZO-1), enhancing vascular permeability	[45]
miR-23a	Nasopharyngeal carcinoma	Promotes tumor angiogenesis	Promotes endothelial cell proliferation, migration, and tube formation; targets and inhibits TSGA10	[46]
miR-210	Leukemia	Promotes tumor angiogenesis	Targets and inhibits Ephrin-A3, activating VEGF/VEGFR2 signaling	[47]
miR-21	Lung cancer	Promotes tumor angiogenesis	Activates STAT3 signaling and upregulates VEGF expression	[49]
miR-23a	Lung cancer	Promotes tumor angiogenesis	Inhibits PHD and tight junction protein ZO-1, increasing vascular permeability	[50]

miR-141-3p	Ovarian cancer	Promotes tumor angiogenesis	Activates JAK-STAT3 signaling in endothelial cells	[51]
miR-9	Nasopharyngeal carcinoma	Promotes tumor angiogenesis	Regulates PDK/Akt signaling to inhibit NPC cell migration	[53]
miR-21	Colorectal cancer	Promotes chemoresistance	Downregulates PTEN and hMSH2, inducing resistance to 5-fluorouracil	[54]
miR-221/222	Breast cancer	Promotes chemoresistance	Inhibits p27 and ER α expression, enhancing tamoxifen resistance	[55]
miR-208b	Colorectal cancer	Promotes chemoresistance	Targets PDCD4 to promote Treg activation, increasing oxaliplatin resistance	[56]
miR-196a	Head and neck cancer	Promotes chemoresistance	Targets CDKN1B and ING5, promoting proliferation, inhibiting apoptosis, and enhancing cisplatin resistance	[59]
miR-222-3p	Ovarian cancer	Promotes immune suppression	Targets SOCS3 and activates STAT3 signaling, inducing M2 macrophage polarization	[65]
miR-301a-3p	Pancreatic cancer	Promotes immune suppression	Inhibits PTEN and activates PI3K γ signaling, driving M2 macrophage polarization	[66]
miR-21,miR-29	Non-small cell lung cancer	Promotes immune suppression	Activates TLR-mediated NF- κ B signaling, inducing a pro-tumor inflammatory microenvironment	[68]
miR-212-3p	Pancreatic cancer	Promotes immune suppression	Inhibits RFXAP expression, reducing MHC II levels and inducing immune tolerance	[69]
miR-20a	Breast cancer	Promotes immune suppression	Downregulates NKG2D ligands (MICA and MICB), reducing NK cell recognition and killing ability	[70]
miR-24-3p	Nasopharyngeal carcinoma	Promotes immune suppression	Targets PTEN, activates PI3K/Akt pathway, and upregulates PD-L1, inhibiting T-cell function	[73]
miR-144	Lung cancer	Promotes tumor metabolism	Upregulates GLUT1, increasing glucose	[75]

			uptake and lactate production	
miR-21	Non-small cell lung cancer	Promotes tumor metabolism	Increases intracellular lipid content and upregulates key lipid metabolism enzymes (FASN, ACC1, FABP5)	[76]
miR-328-3p	Ovarian cancer	Promotes autophagy	Targets Raf1 and inhibits mTOR pathway activation	[81]
miR-425	Non-small cell lung cancer	Promotes autophagy	Targets AKT1 to activate autophagy	[83]
miR-1910-3p	Breast cancer	Promotes autophagy	Targets MTMR3 and activates NF- κ B signaling	[84]
miR-378a-3p	Breast cancer	Maintains CSC stemness	Activates Wnt/Notch pathway	[89]
miR-454	Breast cancer	Maintains CSC stemness	Activates PRRT2/Wnt axis	[90]
miR-328-3p	Ovarian CSCs	Maintains CSC stemness	Targets and inhibits DNA damage-binding protein 2	[93]
miR-30b-3p	Glioma CSCs	Mediates CSC therapy resistance	Targets RHOB, reducing apoptosis and enhancing TMZ resistance	[97]
miR-210	Pancreatic CSCs	Mediates CSC therapy resistance	Upregulates MDR1, YB-1, BCRP, and activates mTOR signaling	[99]
miR-155	Breast CSCs	Mediates CSC therapy resistance	Regulates C/EBP- β and suppresses TGF- β , C/EBP- β , FOXO3a, inducing EMT and chemoresistance	[101]

4.1. Promotion of Tumor Growth and Metastasis

Exosomal miRNAs can modulate the expression of oncogenes or tumor suppressor genes in recipient cells, thereby influencing cellular growth processes and promoting tumor metastasis [33]. Zhang et al. uncovered that miR-200b derived from exosomes of colorectal cancer cells can specifically bind to the 3' untranslated region of the tumor suppressor p27, leading to a reduction in p27 expression at the post-transcriptional level and consequently facilitating the growth of tumor cells [34]. TGF- β activated kinase-1 (TAK1) can suppress the onset of hepatocellular carcinoma by regulating the MAPK-JNK signaling pathway. However, miR-584 within exosomes can target TAK1 and its associated signaling cascades, resulting in the downregulation of TAK1 expression and subsequently promoting the growth and metastasis of hepatocellular carcinoma [35]. In glioblastoma, exosomal miR-148a relieves the inhibitory effect of cell adhesion molecule 1 (CADM1) on the STAT3 pathway by targeting CADM1, significantly enhancing the proliferative and invasive metastatic capabilities of tumor cells [36]. In addition to regulating proliferation-related signaling pathways, exosomal miRNAs can also drive tumor progression by interfering with cell cycle checkpoints and apoptotic pathways. Research has demonstrated that miR-1246 disrupts the cell cycle regulatory network by specifically downregulating the expression of cyclin-G2 (CCNG2), thereby augmenting the proliferative capacity of breast cancer cells and inducing chemotherapy resistance [37].

Concurrently, miR-128 in exosomes derived from breast cancer cells can inhibit the initiation of apoptosis in tumor cells by regulating the expression balance of Bcl-2 family proteins (such as the pro-apoptotic factor Bax), thereby enhancing the tumor's metastatic potential [38]. These findings systematically unveil that exosomal miRNAs can promote tumor growth and metastasis through a coordinated, multi-target, and multi-pathway mechanism.

Epithelial-mesenchymal transition (EMT) represents a fundamental biological process driving cancer invasion and metastasis, characterized by distinct molecular alterations including: (1) downregulation of epithelial markers (E-cadherin, β -catenin), (2) upregulation of mesenchymal markers (vimentin, N-cadherin), and (3) loss of cellular polarity with enhanced motility [39]. Exosomes serve as critical EMT mediators by delivering specific miRNAs that modulate tumor invasive potential. Li et al. demonstrated that tumor-derived exosomal miR-21 post-transcriptionally regulates Snail (a master EMT transcription factor), concurrently upregulating vimentin while downregulating E-cadherin expression, thereby markedly enhancing cancer cell migration and invasion [40]. Wang's group revealed that CCRCC stem cell-secreted exosomal miR-19b-3p suppresses PTEN (a tumor suppressor) expression in recipient cells, effectively inducing EMT and promoting metastatic dissemination [41]. Under hypoxic conditions, BMSC-derived exosomal miR-193a-3p, miR-210-3p, and miR-5100 promote the invasion of lung cancer cells by inducing EMT through STAT3 signaling activation [42]. Sun et al. demonstrated that exosome-delivered miR-335-5p promotes colorectal cancer (CRC) cell invasion and metastasis by inducing epithelial-mesenchymal transition (EMT) through targeted inhibition of RAS p21 protein activator 1 (RASA1) [43].

4.2. Promotion of Tumor Angiogenesis

Angiogenesis supplies tumor cells with nutrients and oxygen while providing escape routes for metastasis, and is therefore recognized as a critical event in cancer progression [44]. Exosomal miRNAs play pivotal roles in angiogenesis by transmitting pro-angiogenic signals, regulating target gene expression, and activating key signaling pathways. For example, hepatocellular carcinoma (HCC)-derived exosomal miR-103 targets multiple endothelial junction proteins, including VE-cadherin, p120-catenin, and zonula occludens-1, thereby enhancing vascular permeability and promoting tumor metastasis [45]. Exosomal miR-23a secreted by nasopharyngeal carcinoma (NPC) cells not only promotes endothelial cell proliferation, migration, and tube formation but also enhances angiogenesis by targeting and suppressing TSGA10 [46]. Hypoxia, a major driving force of tumor angiogenesis, can modulate the activity of various cytokines, including the expression of exosomal miRNAs. Under hypoxic conditions, leukemia cell-derived exosomal miR-210 is highly expressed and promotes endothelial angiogenic activity by targeting Ephrin-A3 and activating the VEGF/VEGFR2 signaling pathway [47]. Further studies have shown that hypoxia upregulates the expression of tissue inhibitor of metalloproteinases-1 (TIMP-1), which in turn activates the PI3K/AKT/HIF-1 signaling pathway to promote miR-210 transcription. By suppressing its target proteins, miR-210 enhances the pro-angiogenic capacity of exosomes derived from TIMP-1-overexpressing cells [48]. In addition, exosomal miR-21 can induce STAT3 pathway activation, leading to upregulation of vascular endothelial growth factor (VEGF) expression in recipient cells, ultimately mediating angiogenesis and malignant transformation in human bronchial epithelial (HBE) cells [49]. Exosomal miR-23a from hypoxic lung cancer cells suppresses prolyl hydroxylase (PHD) and the tight junction protein zonula occludens-1 (ZO-1), thereby increasing vascular permeability and enhancing tumor transendothelial migration [50]. Exosomal miRNAs can also directly promote neovascularization by activating angiogenesis-related signaling pathways. In ovarian cancer, small extracellular vesicles (sEVs) secreted by the SKOV-3 cell line are enriched in miR-141-3p, which activates the JAK-STAT3 pathway in endothelial cells and promotes angiogenesis [51]. Mesenchymal stem cell (MSC)-derived exosomal miR-100 regulates the mTOR/HIF-1 α /VEGF axis to stimulate angiogenesis in breast cancer [52]. In NPC, exosomal miR-9 modulates the

phosphoinositide-dependent kinase (PDK)/Akt pathway to inhibit NPC cell migration and angiogenesis [53].

4.3. Promotion of Tumor Chemoresistance

Chemoresistance is a major cause of therapeutic failure and poor prognosis in cancer patients, primarily driven by tumor cell heterogeneity and remodeling of the tumor microenvironment. Exosomal miRNAs play critical roles in the initiation and progression of chemoresistance. Tumor cells can transfer drug resistance-associated miRNAs to drug-sensitive cells via exosomes, thereby directly regulating target gene expression and inducing resistance. For example, in colorectal cancer, exosomal miR-21 derived from resistant cells induces resistance to 5-fluorouracil (5-FU) by downregulating PTEN and hMSH2 expression [54], whereas in breast cancer, exosomal miR-221/222 from tamoxifen-resistant cells suppresses p27 and ER α expression, thereby enhancing tamoxifen resistance in recipient cells [55]. In addition, exosomal miRNAs can promote drug efflux by regulating the expression of drug transporters, further exacerbating resistance. Tao et al. [56] reported that, in colorectal cancer, exosomal miR-208b targets PDCD4 to promote the activation of regulatory T cells (Tregs), indirectly enhancing tumor resistance to oxaliplatin. Exosomal miRNAs can also inhibit chemotherapy-induced apoptosis by degrading or repressing the mRNAs of pro-apoptotic genes, thereby reducing drug sensitivity. For instance, miR-155 is upregulated in multiple cancers and suppresses PTEN and Fas ligand expression, thus blocking apoptotic signaling and decreasing chemosensitivity [57,58]. In head and neck cancer, cancer-associated fibroblast (CAF)-derived exosomal miR-196a targets CDKN1B and ING5, promoting cell proliferation and inhibiting apoptosis, which confers cisplatin resistance to recipient cells [59]. Moreover, exosomal miRNAs can enhance drug resistance by promoting EMT. Studies have shown that miR-21 and miR-27a are upregulated in pancreatic cancer [60] and breast cancer [61,62], where they suppress E-cadherin and induce the expression of N-cadherin and vimentin, thereby promoting the EMT process and consequently enhancing chemoresistance and metastatic potential.

4.4. Promotion of Tumor Immunosuppression

Tumor cells can suppress the maturation and differentiation of immune cells, remodel the immunosuppressive microenvironment, and induce immune tolerance, thereby establishing a synergistic regulatory network that facilitates malignant progression. As critical carriers of intercellular communication, exosomal miRNAs can reprogram immune regulators and effector cells, including tumor-associated macrophages (TAMs), dendritic cells (DCs), natural killer (NK) cells, and T lymphocytes [63]. TAMs are central components of the tumor microenvironment, with the M1 phenotype exerting antitumor activity, whereas the M2 phenotype promotes tumor growth and metastasis by creating an immunosuppressive niche [64]. Ying et al. [65] reported that exosomal miR-222-3p derived from epithelial ovarian cancer (EOC) cells targets and suppresses SOCS3, activates the STAT3 signaling pathway, and drives macrophage polarization toward a tumor-promoting M2 phenotype, thereby enhancing EOC proliferation and metastasis. Under hypoxic conditions, pancreatic cancer (PC) cell-derived exosomal miR-301a-3p suppresses PTEN and activates the PI3K γ signaling pathway, similarly inducing M2 macrophage polarization [66]. DCs initiate T-cell-mediated immune responses through antigen processing and presentation. Their pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), are activated upon recognition of pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), triggering innate immune signaling cascades [67]. Exosomal miR-21 and miR-29a from non-small cell lung cancer (NSCLC) can activate NF- κ B in a TLR-dependent manner, inducing a tumor-promoting inflammatory microenvironment that drives tumor growth and metastasis [68]. Ding et al. [69] demonstrated that pancreatic cancer cell-derived exosomal miR-212-3p downregulates the expression of regulatory factor X-associated protein (RFXAP), leading to reduced levels of the antigen-presenting molecule MHC class II and the induction of immune tolerance. Exosomal miRNAs can also facilitate immune evasion by impairing immune cell

cytotoxicity. NK cells typically recognize and eliminate tumor cells via the NKG2D receptor–ligand interaction. However, high levels of exosomal miR-20a can downregulate NKG2D ligands (MICA and MICB), thereby weakening NK cell recognition and cytotoxicity, ultimately promoting immune escape and enhancing the metastatic capacity of breast cancer cells [70]. In nasopharyngeal carcinoma (NPC), exosomal miRNAs can concurrently inhibit T-cell proliferation and differentiation by targeting the MAPK1 and JAK/STAT signaling pathways, thereby facilitating tumor progression [71]. T helper 1 (Th1) cells, a differentiated subset of naïve CD4⁺ T cells, secrete IFN- γ , a key effector molecule in antitumor immunity. Exosomal miR-let-7d suppresses Th1 cell proliferation and IFN- γ production, inducing tumor immune tolerance [72]. Furthermore, exosomal miR-24-3p can target PTEN, activate the PI3K/AKT signaling pathway, and upregulate PD-L1 expression, thereby inhibiting T-cell function and promoting NPC malignant progression [73].

4.5. Promotion of Tumor Metabolism

Exosomal miRNAs can modulate the expression or activity of metabolic enzymes and reprogram tumor cell metabolic pathways, thereby influencing energy supply, biosynthetic processes, and ultimately regulating tumor growth and metastasis. In glycolysis, exosomal miRNAs can target key rate-limiting enzymes. For instance, Jiang et al. [74] reported that miR-143 suppresses glycolysis by targeting hexokinase 2 (HK2), whereas miR-155 indirectly upregulates HK2 expression by inhibiting miR-143, thereby enhancing glycolysis and promoting tumor cell proliferation. Glucose transporters (GLUTs) are essential for glucose uptake, and miR-144 has been shown to upregulate GLUT1 expression in lung cancer, increasing glucose uptake and lactate production, which in turn supports cancer cell growth [75]. Beyond glucose metabolism, exosomal miRNAs also participate in the regulation of fatty acid metabolism. Upregulation of miR-21 in NSCLC cells promotes cell growth and migration, while increasing intracellular lipid accumulation and elevating key lipid metabolic enzymes, including fatty acid synthase (FASN), acetyl-CoA carboxylase 1 (ACC1), and fatty acid-binding protein 5 (FABP5) [76]. Moreover, exosomal miRNAs can regulate the expression of metabolic signaling molecules such as PI3K, AKT, or mTOR, thereby affecting glucose metabolism, lipid biosynthesis, and protein translation. Notably, miR-21 has been reported to activate the PI3K/AKT pathway in colorectal and lung cancers, promoting glycolysis and tumor cell proliferation [77,78]. AMP-activated protein kinase (AMPK) acts as a central energy sensor, activated under low-energy conditions to promote catabolic pathways and maintain energy homeostasis. Evidence suggests that miR-451 may modulate tumor metabolic reprogramming by targeting the AMPK pathway, thereby facilitating tumor growth [79].

4.6. Regulation of Autophagy

Autophagy is a highly conserved cellular self-degradation process that maintains intracellular homeostasis by degrading damaged organelles and misfolded proteins via lysosomes. In cancer, autophagy plays a dual role: on one hand, it suppresses tumor initiation by clearing harmful components; on the other hand, in established tumors, autophagy provides metabolic substrates and energy to cancer cells, promoting their survival, drug resistance, and metastasis [80]. Exosomes can deliver miRNAs to target cells, regulating autophagy-related genes or signaling pathways, thereby influencing the formation, elongation, and degradation of autophagosomes. This process plays a critical role in disease treatment, intercellular communication, and pathophysiological processes. Exosomes secreted by ovarian cancer cells carry miR-328-3p, which targets Raf1 to inhibit the activation of the mTOR signaling pathway, thereby promoting autophagy and enhancing tumor cell invasiveness [81]. miR-224-5p in exosomes derived from human umbilical cord mesenchymal stem cells (hUCMSCs-exo) regulates autophagy by targeting and suppressing HOXA5 expression, affecting the proliferation and apoptosis of breast cancer (BC) cells [82]. In NSCLC, exosomal miR-425-3p activates autophagy in recipient cells by targeting AKT1, ultimately leading to chemoresistance [83]. Wang et al. [84] reported that exosomal miR-1910-3p promotes breast cancer cell proliferation, metastasis, and autophagy by targeting MTMR3 and activating the NF- κ B signaling

pathway. Osteoblast-derived exosomal miR-140-3p targets ACER2 and promotes prostate cancer progression by inhibiting autophagy via the AKT/mTOR pathway [85].

5. Roles of Exosomal miRNAs in Cancer Stem Cells

Exosomal miRNAs can precisely regulate the activity of oncogene promoters and the expression of tumor suppressor genes, thereby significantly influencing multiple functional mechanisms, biological behaviors, and phenotypic characteristics of cancer stem cells (CSCs), as shown in Figure 3. Their core regulatory roles are mainly manifested in: modulating the self-renewal capacity, differentiation direction, invasive and metastatic potential of CSCs, as well as the development of therapeutic resistance.

Role of exosome miRNAs in cancer stem cells

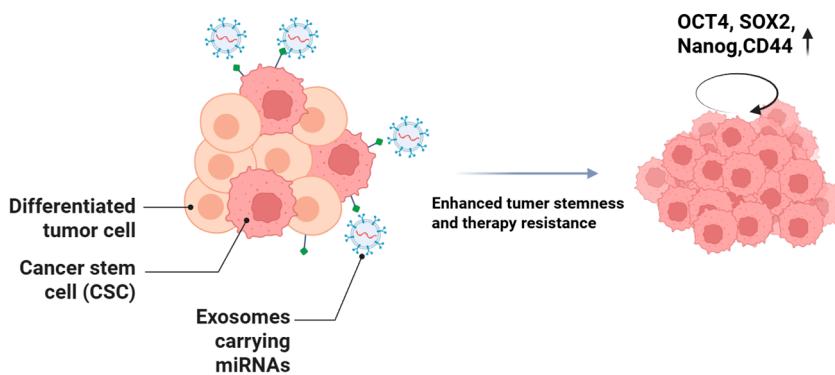


Figure 3. Exosomal miRNAs can enhance the stemness of cancer stem cells (CSCs), which is primarily manifested by increased expression of stemness markers, enhanced tumorsphere-forming ability, and strengthened self-renewal capacity.

5.1. Maintenance of CSC Stemness Characteristics and Self-Renewal

The Wnt, Notch, and Hedgehog signaling pathways are key regulators of tumor stemness [86]. Exosomal miRNAs modulate these pathways to regulate the sphere-forming ability and tumorigenicity of CSCs, thereby maintaining and promoting their stem-like phenotype. Wu et al. found that miR-483-5p promotes proliferation, invasion, and self-renewal of gastric cancer stem cells by activating the Wnt/β-catenin signaling pathway [87]. Under the regulation of the transcription factor HIF-1α, miR-1275 activates both the Wnt/β-catenin and Notch pathways, enhancing stemness in lung adenocarcinoma cells and promoting tumorigenicity, recurrence, and metastasis [88]. Yang et al. [89] reported that chemotherapy activates the EZH2/STAT3 axis in breast cancer cells, leading to secretion of exosomes containing miR-378a-3p, which upon uptake by surviving cells activate Wnt/Notch pathways to enhance stemness and confer drug resistance. Exosomal miR-454 from breast cancer cells maintains CSC stemness in ovarian cancer by activating the PRRT2/Wnt axis [90]. M2 macrophage-derived exosomal miR-27a-3p promotes liver cancer CSC characteristics, proliferation, and tumorigenicity in vivo via activation of the TXNIP pathway [91]. Additionally, exosomal miRNAs target stemness-related gene expression to promote CSC traits. Chemotherapy induces breast cancer cells to secrete exosomes carrying multiple miRNAs such as miR-9-5p, miR-195-5p, and miR-203a-3p, which target ONECUT2, induce CSC phenotypes, and upregulate stemness-associated gene expression [92]. miR-328-3p is significantly upregulated in ovarian CSCs, maintaining stemness by targeting and suppressing DNA damage-binding protein 2. Concurrently, low reactive oxygen species levels reduce ERK signaling activity, favoring enhanced miR-328 expression and CSC maintenance [93].

5.2. Mediation of CSC Therapy Resistance

CSCs are considered key contributors to tumor drug resistance. Increasing evidence shows that CSC-derived exosomes deliver miRNAs to non-CSC cells, promoting chemoresistance through multiple mechanisms including apoptosis regulation, enhanced drug efflux, and induction of drug resistance in chemo-sensitive cells [94–96]. CSC-derived exosomes reprogram recipient cells' cell cycle and apoptosis-related genes to facilitate resistance. Yin et al. [97] demonstrated that under hypoxia, miR-30b-3p in glioma CSC-derived exosomes targets RHOB, reducing apoptosis and promoting resistance to temozolomide. Zhuang et al. [98] reported that exosomal miR-146a-5p from cancer-associated fibroblasts regulates cell cycle and apoptosis pathways, maintaining bladder CSC stemness and enhancing chemoresistance, thus establishing a pro-resistant tumor microenvironment niche. Yang et al. [99] showed that exosomes from gemcitabine-resistant pancreatic CSCs transfer miR-210 to drug-sensitive cells, conferring resistance accompanied by upregulation of MDR1, YB-1, BCRP, and activation of the mTOR pathway, suggesting miR-210 mediates resistance by promoting drug efflux in non-CSC subpopulations. miR-221 suppresses the tumor suppressor QKI by targeting its mRNA 3'-UTR, leading to aberrant activation of downstream stemness pathways, which promotes tumorigenicity and chemoresistance of colorectal CSCs [100]. CSC-derived exosomes transmit miRNAs and other genetic materials that enable horizontal transfer of resistance to sensitive cells. Santos et al. experimentally confirmed that miR-155 secreted by breast CSC exosomes downregulates C/EBP- β and inhibits TGF- β , C/EBP- β , and FOXO3a expression, inducing EMT and chemoresistance in sensitive cells [101]. miR-485-5p specifically suppresses keratin 17 (KRT17) expression, thereby regulating integrin-mediated FAK/Src/ERK signaling and β -catenin nuclear translocation, ultimately affecting oral CSC stemness maintenance and chemoresistance phenotypes [102].

6. Translational Applications of Exosomal miRNAs in Cancer Diagnosis and Therapy

6.1. Potential Diagnostic and Prognostic Biomarkers

Exosomal miRNAs, owing to their remarkable stability, high tissue and disease specificity, and widespread presence in various body fluids, are regarded as promising diagnostic and prognostic biomarkers with significant clinical potential [103]. They have demonstrated important value in the detection and evaluation of malignancies, neurological disorders, and cardiovascular diseases. Wu et al. [104] examined the expression profiles of eight serum and serum-derived exosomal miRNAs (including miR-21-5p and miR-141-3p) in healthy individuals, patients with benign lung lesions, and patients with early-stage (NSCLC, stage I/II). Their findings revealed that serum exosomal miRNAs outperformed serum miRNAs as biomarkers for early NSCLC diagnosis, and the combination of both further enhanced diagnostic accuracy. Wang et al. [84] reported that the combination of CA15-3 in exosomes and serum miR-1910-3p served as an effective biomarker, improving the reliability of breast cancer diagnosis. In prostate cancer patients, plasma exosomal miR-141-5p was upregulated, while miR-125a-5p was downregulated, suggesting their potential as diagnostic indicators [105]. In oral squamous cell carcinoma (OSCC), elevated plasma exosomal miR-130a levels were identified as independent predictors of overall survival and recurrence-free survival [106]. Liu et al. [107] demonstrated that serum exosomal miR-106b-3p was significantly increased in metastatic CRC compared to non-metastatic cases, indicating its potential as a prognostic biomarker and therapeutic target. Additionally, urinary exosomal miR-155-5p, miR-15a-5p, and miR-21-5p were markedly elevated in bladder cancer patients compared to healthy controls, supporting their utility as non-invasive diagnostic indicators [108].

6.2. Potential Therapeutic Targets

6.2.1. Targeted Delivery of Exosomal miRNAs to Tumor Cells

Exosomes can be engineered to encapsulate specific tumor-suppressive miRNAs for precise delivery to target cells, offering novel therapeutic strategies. For instance, miR-122 loaded into MSC-derived exosomes effectively targeted hepatocellular carcinoma cells, exerting anti-tumor effects [109]. miR-375, a tumor suppressor inversely correlated with EMT, was delivered via tumor-derived exosomes in the form of mimics by Rezaei et al. [110], thereby suppressing migration and invasion in colon cancer cells. In gastric cancer, CAF-derived exosomes loaded with miR-139 or miR-34 mimics significantly inhibited tumor cell proliferation and metastasis [111,112]. Similarly, miR-205 mimics transfected into bone marrow mesenchymal stem cell-derived exosomes suppressed RHPN2 expression, impeding prostate cancer progression [113]. In a recent study, Cui et al. [114] employed electroporation to load miR-486-5p into bone marrow mesenchymal stem cell-derived exosomes and deliver them specifically to tumor sites. The results demonstrated that this strategy effectively inhibited glycolysis and stemness in colorectal cancer cells by targeting NEK2, thereby significantly suppressing tumor growth and progression. In addition to delivering tumor-suppressive miRNAs, exosomes can serve as carriers for miRNA inhibitors or antagonists to block oncogenic miRNA activity. This can be achieved using anti-miRNA oligonucleotides or inhibitors that interfere with transcription, processing, or stability. For example, Wang et al. [115] encapsulated a miR-21 inhibitor into engineered exosomes and delivered it to gastric cancer cells, achieving greater inhibitory effects and lower cytotoxicity compared to conventional transfection methods. Liang et al. [54] co-loaded the chemotherapeutic drug 5-FU and a miR-21 inhibitor (miR-21i) into exosomes for targeted delivery to Her2-positive colorectal cancer and 5-FU-resistant cell lines. This approach restored the function of tumor suppressor PTEN and DNA repair protein hMSH2, inducing cell cycle arrest and apoptosis. Furthermore, transfection of an miRNA-BART1-5p antagonist into exosomes significantly inhibited angiogenesis in tumor tissues and induced apoptosis [116]. Collectively, these studies highlight the substantial potential of exosomes in miRNA-based targeted cancer therapy, offering novel strategies and insights for precision oncology.

6.2.2. Targeted Delivery of Exosomal miRNAs to Cancer Stem Cells

The maintenance of CSC stemness is highly dependent on the regulation of multiple signaling pathways within the tumor microenvironment. As essential intercellular communication vehicles, exosomes can deliver specific miRNAs to CSCs, modulating various stemness-related signaling pathways and thereby altering their biological properties to suppress tumor growth and progression. In recent years, the advent of engineered exosomes has provided a feasible and efficient strategy for targeted miRNA delivery to CSCs. Epithelial cell adhesion molecule (EpCAM) is one of the classic CSC markers. Studies have shown that engineering exosomes to specifically recognize and target EpCAM-expressing liver CSCs, while loading them with β -catenin-specific siRNA, can effectively block activation of the Wnt/ β -catenin signaling pathway and significantly inhibit CSC proliferation [117]. Similarly, tumor-suppressive miRNAs can be loaded into exosomes for CSC targeting. For example, Alessia et al. [118] demonstrated that exosomes derived from human liver stem cells (HLSCs) can deliver miR-145 and miR-200 to renal CSCs, inducing apoptosis and markedly suppressing proliferation, sphere-forming capacity, and invasiveness. SOX9, a critical regulator of CSC stemness maintenance, self-renewal, and tumor progression, has emerged as an important therapeutic target for CSC-directed interventions. Wu et al. [119] reported that bone marrow mesenchymal stem cell-derived exosomes carrying miR-145-5p specifically target SOX9 in non-small cell lung cancer, thereby significantly impairing CSC stemness maintenance and inhibiting tumor cell proliferation, migration, and invasion. In addition, Lang et al. [120] demonstrated that transducing miR-124a into MSCs enables the generation of miR-124a-enriched exosomes (Exo-miR-124a), which can be effectively delivered to glioblastoma stem cells (GSCs). In vitro, Exo-miR-124a markedly reduced GSC viability and clonogenic potential, while in an orthotopic GSC xenograft mouse model,

systemic administration of Exo-miR-124a resulted in 50% of tumor-bearing mice achieving long-term tumor-free survival, indicating complete tumor eradication. Beyond tumor-suppressive miRNAs, engineered exosomes can also be utilized to deliver inhibitors of pro-stemness miRNAs (anti-miRs) to attenuate CSC tumorigenicity. For instance, Naseri et al. [121] employed electroporation to load anti-miR-142-3p into exosomes for targeted delivery to tumor sites, effectively suppressing endogenous miR-142-3p expression and function. This intervention disrupted signaling pathways associated with breast CSC tumorigenicity, significantly reducing CSC tumorigenic potential and impeding malignant progression of breast cancer.

7. Conclusions and Future Perspectives

Exosome-derived miRNAs, as key mediators of intercellular communication, play crucial roles in cancer and CSC biology by reshaping the tumor microenvironment, regulating CSC stemness maintenance, and modulating therapeutic resistance. They are deeply involved in tumor initiation and progression, metastasis, and treatment resistance. Moreover, the detectability and specificity of exosomal miRNAs in liquid biopsies provide a solid foundation for their use as biomarkers for early cancer diagnosis, therapeutic response assessment, and prognostic prediction. In recent years, strategies employing engineered exosomes as miRNA delivery vehicles have achieved promising results in preclinical studies, offering new therapeutic avenues for targeting CSCs and overcoming drug resistance. However, several challenges remain in this field. First, the mechanisms underlying exosomal miRNA biogenesis, selective packaging, and secretion are not yet fully elucidated, limiting their precise application in early disease diagnosis. Second, the techniques for exosome isolation and purification, miRNA loading efficiency, and targeted *in vivo* delivery still require optimization to ensure safety and controllability. Furthermore, the functions of exosomal miRNAs within CSCs and the tumor microenvironment are highly context-dependent and exhibit spatiotemporal specificity, adding complexity to clinical translation. Future research should focus on the following directions: Elucidating the dynamic regulatory networks of exosomal miRNAs in CSC stemness maintenance and tumor progression; Developing efficient, standardized techniques for exosome isolation and quantitative miRNA detection to improve reproducibility and accuracy in clinical testing; Advancing the application of engineered exosomes in miRNA-targeted delivery by optimizing loading efficiency and targeting specificity to achieve CSC-specific eradication; Integrating single-cell omics, multi-omics, and spatial transcriptomics to uncover the key mechanisms by which exosomal miRNAs regulate tumor heterogeneity and resistance evolution; Accelerating the clinical translation of exosomal miRNA-based diagnostic and therapeutic strategies, grounded in rigorous safety evaluations. In summary, research on exosome-derived miRNAs in cancer and CSCs is evolving from fundamental mechanistic studies toward clinical application. With deeper insights into their molecular mechanisms and the refinement of engineering-based delivery technologies, exosomal miRNAs are poised to become integral components of future precision oncology, offering innovative solutions to the challenges of tumor recurrence, metastasis, and therapeutic resistance.

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