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REVIEW

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Exosomal miRNAs: the tumor's trojan horse in selective metastasis

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Abstract

Organs of future metastasis are not passive receivers of circulating tumor cells, but are instead selectively and actively modified by the primary tumor before metastatic spread has even occurred. Tumors orchestrate a pre-metastatic program by conditioning distant organs to create microenvironments that foster the survival and proliferation of tumor cells before their arrival, thereby establishing pre-metastatic niches. Primary tumor-derived exosomes modulate these pre-metastatic niches, generating a permissive environment that facilitates the homing and expansion of tumor cells. Moreover, microRNAs have emerged as a key component of exosomal cargo, serving not only to induce the formation of pre-metastatic niches but also to prime these sites for the arrival and colonization of specific secondary tumor populations. Against this backdrop, this review endeavors to elucidate the impact of tumor-derived exosomal microRNAs on the genesis of their individualized pre-metastatic niches, with a view towards identifying novel means of specifying cancer metastasis and exploiting this phenomenon for cancer immunotherapy.

Keywords Selective Metastasis, Pre-metastatic Niche, Exosomes, MicroRNA

Introduction

Metastasis, a terminal stage of cancer progression characterized by the aberrant migration and colonization of tumor cells in distant organs, represents a profound and debilitating hallmark of cancer pathophysiology. This phenomenon frequently culminates in suboptimal therapeutic outcomes and exacerbates patient mortality. Despite a plethora of investigations into the underlying mechanisms, the metastatic cascade remains shrouded in complexity, with numerous aspects remaining poorly understood and in need of further elucidation [1–3]. The successful colonization of circulating tumor cells (CTCs) in secondary or distant organs represents a pivotal step in the metastatic process. However, this process is profoundly influenced by the local microenvironment of the target organ, which can either facilitate or impede tumor cell colonization [4].

To unravel the intricate molecular mechanisms governing cancer metastasis, Chaffer and Weinberg have posited a two-stage paradigm; the initial phase encompasses the physical dissemination of malignant cells from the primary tumor to the secondary tissue microenvironment, thereby initiating the metastatic cascade. This inaugural step is followed by a subsequent phase, which involves the colonization of these disseminated cells, requiring their successful adaptation to the novel tissue context and establishment of a self-sustaining population [3].

Primary tumors have been found to modulate the microenvironment of distant organs prior to CTC arrival, thereby establishing a pre-metastatic niche that primes the subsequent colonization of disseminated tumor cells [4]. A diverse array of molecular and cellular constituents has been pinpointed as critical mediators of pre-metastatic niche formation across various tumor models. These niche-inducing molecules are secreted by tumor cells, myeloid cells, and stromal cells, functioning

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in concert to initiate, polarize, and establish a pre-metastatic niche in distant organs, thereby generating a permissive environment for metastatic colonization [5, 6].

The extracellular vesicles derived from the tumor microenvironment assume a pivotal role in the formation of pre-metastatic niches within specific organs. Exosomes, small membrane-bound vesicles that are part of the extracellular vesicle population, play a vital role in pre-metastatic niche formation by functioning as a means of intercellular communication between tumor cells and their surrounding microenvironment. These extracellular vesicles are capable of transferring various biomolecules, including proteins, mRNAs, microRNAs, small RNAs, and DNA fragments, to recipient cells through a process known as horizontal gene transfer. This phenomenon enables the exchange of molecular information between tumor cells and their surroundings, thereby facilitating the establishment of a pre-metastatic niche [6]. Notably, microRNAs (miRNAs) assume a pivotal role in the multifaceted process of tumor growth and metastasis, encompassing all stages of carcinogenesis. Aberrant miRNA expression patterns are a hallmark of cancer cells, with numerous cancer types exhibiting either elevated or diminished miRNA levels. Cancer-secreted exosomes also display aberrant miRNA profiles, which can contribute to the creation of a permissive environment for tumorigenesis. By modulating the expression of oncogenes and/or tumor suppressor genes in recipient cells, these miRNAs can influence cellular processes and promote tumorigenesis. This underscores the potential significance of miRNA-containing exosomes as a key mechanism by which cancer cells exert their influence on the microenvironment, ultimately facilitating the development of cancer [7].

Selective metastasis

Cancer metastasis refers to the process through that cancer cells spread from the main tumor, settle, and develop at a location beyond the primary tumor site. For this purpose, cancer cells need to detach from their primary site and enter the bloodstream or lymphatic system. Once in circulation, they must survive the rigors of travel, including the immune response and blood flow, to reach their secondary sites [8–11]. At these new sites, they must adapt to their new environment by undergoing further changes that allow them to grow and thrive [12].

Captivatingly, most cancer types appear to have preferential locations to colonize, confirming that the spread of metastases is not random [12]. In fact, certain tissue microenvironments, known as "anti-metastatic niches," are found to be inhospitable for formation of secondary tumor [4]. The metastatic localization of cancer cells is a complex process orchestrated by a multitude of pivotal mediators, including chemokines and secreted proteins. Another critical determinant of successful metastasis is the ability of metastatic cells to survive and adapt in their new environment. To enable successful engraftment, the secondary environment must undergo modifications to create a permissive microenvironment for cancer cell colonization (Fig. 1) [12]. Tumor-secreted factors, including tumor-derived extracellular vesicles and particles, circulate in the bloodstream and modulate distant organs, thereby influencing metastatic progression. Primary tumors can induce early changes in the microenvironment of secondary organs devoid of cancer cells, creating a permissive environment conducive to cancer cell settlement and metastasis initiation. This phenomenon gives rise to pre-metastatic niches (PMNs), which provide a fertile ground for the establishment of metastatic foci, preceding the arrival of cancer cells [4]. The seed and soil hypothesis, posits that cancer cells (the seeds) require a receptive microenvironment (the soil) for engraftment during metastasis [12]. It is established that the primary tumor can trigger the perpetuation of pre-metastatic niches (soil) through a process analogous to irrigation, where the tumor acts as the "watering can" that nourishes the soil, allowing it to become receptive to seed colonization.

The PMN is shaped by intricate interactions between cancer-secreted factors and resident stromal cells at distant sites, as well as bone marrow-derived cells (BMDCs). The priming of a distant organ comprises a stepwise process that subverts tissue homeostasis, creating an environment receptive to circulating tumor cell (CTC) colonization. This multifaceted process involves the induction of vascular leakiness, lymphangiogenesis, extracellular matrix (ECM) remodeling, and the generation of an immunosuppressive microenvironment. These alterations collectively create a permissive environment that enables CTCs to establish a foothold and initiate metastatic growth [4]. It has been reported that the exosomes derived from tumor cells that are capable of migrating have the ability for interacting with blood vessels, stromal components, and immune cells to establish a pre-metastatic niche [13]. Therefore, the mechanisms by which tumor-derived exosomes subserve the tumor are still being investigated. Through the next section, we will delve into the most recent discoveries regarding the impact of cancer cell-derived exosomes and the miRNAs they transport, as one of the most important cargos, on selective and distant metastasis.

Role of cancer cells-derived exosomal miRNAs in selective metastasis

The metastatic potential of cancer cells is contingent upon a dynamic crosstalk between the tumor cells and their microenvironment (TME), where the tumor influences the microenvironment, which in turn shapes

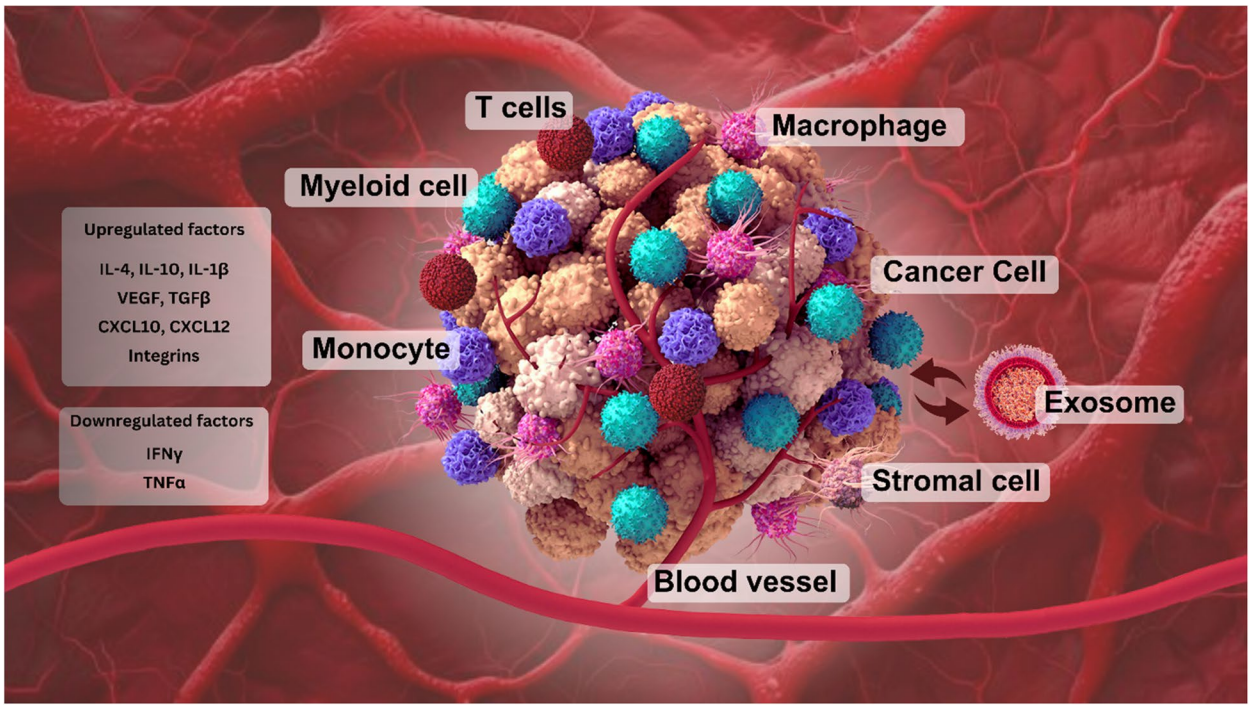

Fig. 1 Illustration of tumor microenvironment. Diverse range of cell types exist in tumor microenvironment, including immune cells, stem cells, and other cell subtypes that interact and influence tumor growth and progression

the behavior of cancer cells [14]. Moreover, it is conformed that the establishment of a pre-metastatic niche is orchestrated by the secretion of soluble factors from the primary tumor into the systemic circulation. Among these factors, tumor-derived exosomes (TDEs) are of particular significance, as they are small extracellular vesicles that encapsulate a diverse range of biomolecules, including RNA, DNA, proteins, metabolites, and microRNAs, derived from their parent cells [15, 16].

Liu and Cao have identified six key features of the pre-metastatic niche that facilitate tumor cell colonization and metastasis: inflammation, immunosuppression, organotropism, reprogramming, lymphangiogenesis, angiogenesis, and vascular permeability. These features collectively regulate the colonization and survival or dormancy of circulating tumor cells upon arrival in the target organ, influencing the ultimate fate of these disseminated cells [6]. Various studies have confirmed the contribution of exosomes in cancer metastasis, through their role in formation of the premetastatic niche, influencing tumor cells and TME, and determining specific organotropic metastasis [17, 18]. TDEs exhibit a predilection for homing to highly vascularized tissues, such as the lung and liver, owing to their distinctive surface integrin profiles [15]. Specifically, TDEs interact with inflammatory molecules to facilitate the formation of the PMN. Moreover, TDEs exert a multifaceted influence on the establishment of the PMN, encompassing immunosuppression and immune surveillance, promotion of angiogenesis and vascular permeability, activation of stromal cells, and remodeling of the extracellular matrix (ECM), as well as organotropic metastasis [19]. Given their ubiquity in bodily fluids and their potential as non-invasive biomarkers for cancer diagnosis, TDEs are being extensively explored as a novel therapeutic target in clinical settings [15].

There has been an increasing focus on the role of TDEs in mediating complex intratumoral communications within the tumor microenvironment [20]. TDEs have been shown to modulate tumor progression by secreting pro-inflammatory cytokines, promoting angiogenesis, triggering Toll-like receptor 3 (TLR-3)-dependent neutrophil infiltration, and recruiting myeloid-derived suppressor cells (MDSCs) [21]. The non-coding RNA cargo of TDEs, particularly microRNAs has been increasingly recognized as a critical component of the PMN. In fact, the intricate dialogue between tumor cells and the microenvironment is orchestrated by a complex interplay of signaling pathways, wherein miRNAs assume a pivotal role in shaping the pre-metastatic niche. TDEs have been shown to transfer miRNAs to surrounding cells or cells in distant metastatic niches by conditioning the pre-metastatic tumor microenvironment (TME) [14, 22]. Tumor-derived miRNAs selectively target key genes

involved in immune cell suppression, angiogenesis, and EMT, thereby priming the pre-metastatic niche in distant organs (Fig. 2). This miRNA-mediated signaling cascade enables the primary tumor to establish a permissive environment for subsequent metastasis. Furthermore, organ-specific miRNA profiles play a crucial role in directing metastasis to specific tissues by regulating gene expression and modulating cellular processes [23, 24]. In fact, detection of specific miRNAs may serve as a potential biomarker for predicting or prognosticating metastasis, thereby providing a means to prevent or delay its onset [15, 19, 25, 26].

With that context, through this section we will delve into the pivotal role of exosomal miRNAs in orchestrating organ-specific metastasis and PMN establishment across various cancer types, thereby highlighting the intricate molecular mechanisms underlying the heterogeneous patterns of tumor dissemination.

Colorectal cancer

Colorectal cancer (CRC) is the third most prevalent cancer globally. Despite advances in treatment, CRC has a significant mortality rate, with approximately 56% of patients succumbing to their disease. Notably, approximately 20% of patients present with metastatic disease at the time of diagnosis, a phenomenon that has remained relatively stable over the past two decades [27]. The most frequent sites of metastasis from CRC are the liver, lung,

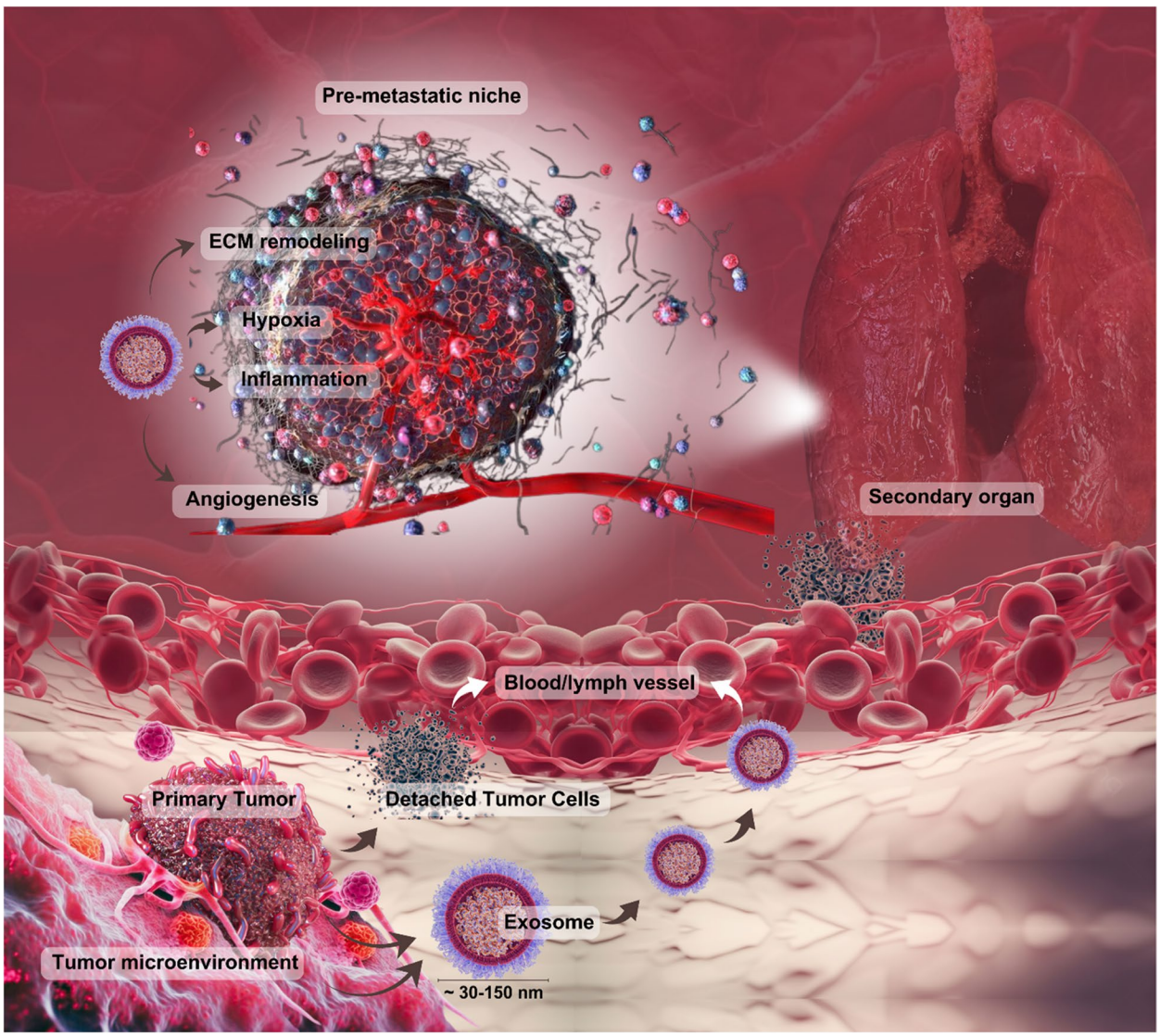

Fig. 2 The effect of tumor microenvironment in preparation of pre-metastatic niche. Exosomal microRNA derived from tumor cells and tumor microenvironment can alter pre-metastatic niche in favor of tumor metastasis

peritoneum, brain, and bone, with less common metastasis to the adrenal glands and spleen (Fig. 3) [28].

Exosomes derived from CRC cells can contain oncogenic miRNAs that suppress EMT inhibitors and triggers CRC metastasis [29]. For example, exosomal miR-335-5p originated from metastatic CRC cells are found to induce CRC metastasis through enhancing EMT by targeting RASA1 [30] and DLC-1 [31]. Besides, EMT-CRC-secreted exosomal miR-27b-3p triggers metastasis by inducing EMT through targeting p120 and vascular endothelial cadherin (VE-Cad) CRC cells [32]. In addition, exosomal components can be originated from or delivered to tumor cells or cells within the tumor microenvironment, elevating the metastatic activity through triggering the EMT process in tumor cells and effecting the microenvironment's characteristic [29]. For instance, EMT-CRC-derived exosomal miR-29a enhances metastasis in endothelial cells in the TME by targeting KLF4 [33].

Furthermore, tumor-derived exosomes within serum can deliver miRNAs to distant sites and trigger metastasis. Altered regulation of exosomal miRNAs can promote metastatic cascade through upregulating EMT markers and phenotypic features of pro-metastatic cells. MiR-221/222-3p is an onco-miRNA that is associated with poor prognosis in CRC individuals [34, 35]. Recently, Tian et al. [36] reported exosomal miR-221/222-3p secreted from CRC cells enhances liver metastasis by positively increasing the expression level of hepatocyte growth factor through inhibiting SPINT1. Furthermore, exosomes originated from HCT116-TP53(R273H) cells are adsorbed by mouse embryonic fibroblasts (MEFs) and became activated. Furthermore, it has been shown that miR-21-3p and -769-3p are capable of activating

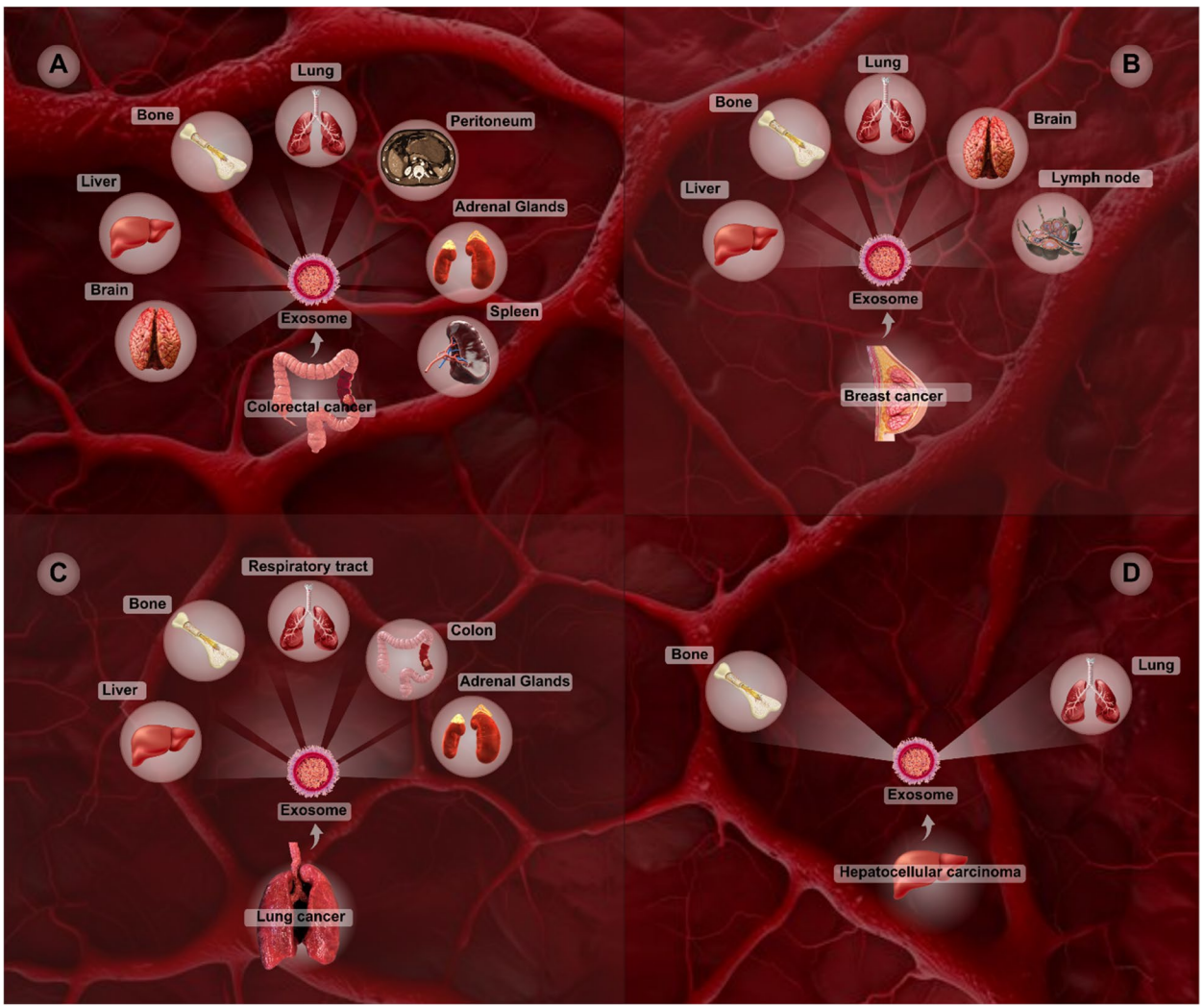

Fig. 3 The effect of tumor-derived exosomes in selective metastasis. Organotropism in **A** colorectal cancer, **B** breast cancer, **C** lung cancer, **D** hepatocellular carcinoma

fibroblasts and exerting a synergistic influence on the transforming growth factor-β (TGF-β)/Smad axis through their target genes. Overall, the mutant p53 CRC cells-derived exosomal miR-21-3p and -769-3p enhances pulmonary metastasis by activating stromal fibroblasts and premetastatic niche. In return, activated fibroblasts promotes tumor cell EMT by positively regulating TGF-β [37]. Exosomal miR-106b-3p derived from high invasive potential CRC cells contributes to lung metastasis in mice by targeting DLC-1 [31].

Immunosuppression is a critical factor for forming and developing the PMN and development of PMN, and the main contributor to tumors survival and development in vivo. plasma-derived exosome miR-203 is demonstrated to promote the differentiation of monocytes in distal organs into M2 TAMs of immunosuppressant phenotype [38]. Meanwhile, it has been established that exosomal miR-934 can induce the differentiation of normal phenotype M1 into M2 TAMs [39]. Downregulation of SOCS3 through miR-222-3p in TDEs is established to promote STAT3-mediated M2 and contribute to the immunosuppressive microenvironment [40]. Moreover, the upregulatory effect of exosomal miR-425-5p and -25-3p on M2 TAMs expression through the PI3K/AKT axis, have been demonstrated to trigger distant metastasis in CRC [41].

Noteworthy, inflammation is found to be implicated in suppression of the tumor progression as well as promotion of tumor occurrence and metastasis. For instance, inflammatory M1 TAMs are found to contribute to CRC development in colitis through their capability to have pro-inflammatory and immunostimulatory activity as well as producing anti-tumor factors, including IL-1β, IL-6 and TNF-α [42]. Hence, during tumor growth and metastasis, chronic inflammation that is the foundation of inflammatory microenvironment, can trigger the PMN formation in distant organs [43]. In fact, the aforementioned pro-inflammatory cytokines serve a crucial role in inflammatory microenvironment, which promotes tumor survival, proliferation and metastasis [43]. It has been established that low-density IL-1β can induce the local inflammatory response and result in protective immune responses, whereas high densities can trigger the inflammation-related cancer tissue damage [44]. On the other hand, during the immune response, IL-6 can activate T and B cells to perform an anti-inflammatory role [45]. It has been demonstrated that exosomal miRNAs derived from CRC tumor cells can upregulate IL-6 secretion, therefore elevating inflammatory responses [46]. In fact, high concentration of IL-6 has been identified in serum, live tumors or biopsies of cancer individuals, confirming that the inflammatory effects of this cytokine might be associated with the cancer occurrence [47]. Exosomal miR-21 can trigger the release of pro-inflammatory IL-6 and IL-21 and their presence within circulation, thereby promoting the formation of an inflammatory microenvironment [48]. More studies are shown in Tables 1 and 2.

In conclusion, the identification of specific exosomal microRNAs that promote EMT and tumor invasiveness, as well as those that contribute to immunosuppression and inflammation, may lead to the development of innovative therapeutic strategies aimed at disrupting these pathways and inhibiting CRC progression.

Breast cancer

Invasive breast cancer often exhibits a propensity for lymphatic and distant metastasis. At early-stage metastasis breast cancer, dissemination of tumor cells through both lymphatic and hematogenous systems occurs [14]. Multiple organs including lymph nodes, bone, lungs, brain, and liver are often found as receiver of the breast cancer metastasis (Fig. 3) [14]. The aberrant downregulation of miR-130a-3p has been identified in human breast cancer tissues and exosomes from circulating blood. The lower levels of exosomal miR-130a-3p are also found to be related to lymph node metastasis and advanced TNM stage [159]. In vitro study has established that exosomal miR-130a-3p can inhibit the cell proliferation, migration, and invasion of human breast cancer stem cells (BCSCs) through regulation of RAB5B/epidermal growth factor receptor signaling pathways [160]. Moreover, it has been established that exosomal miR-770 can be transmitted into tumor-associated macrophages, and subsequently increase the expression of miR-770 in macrophages [160]. In addition, upregulation of miR-770 is established to suppress the invasion and migration of Triple-negative breast cancer (TNBC) through targeting STMN1. On the other hand, Let-7a and c-Myc exhibit a negative correlation with BC. The exosomal Let-7a originated from MDA-MB-231 cell can suppress the proliferation, migration, and invasion both in vitro and in vivo through downregulating the c-Myc expression [161]. Moreover, it has been demonstrated that miR-188-5p can suppress breast cancer-cell proliferation and migration, through targeting IL-6 signal transducer (IL6ST) [162]. This data have confirmed the selective sorting of miR-188-5p into exosomes from malignant BC cells [14].

In the process of metastatic and diffusion, BC gains the capability to transmigrate through blood vessels via promoting alteration within the endothelial barrier [14]. Exosomal miR-939 in TNBC cells elevated tumor cell trans-endothelial migration and directly targeted vascular endothelial cadherin (VE-cadherin) in endothelial cells [163]. This suggests that BC-secreted exosomal miR-939 is implicated in the extracellular pro-tumorigenic characteristic and is correlated with

Table 1 Role of Exosomal miRNAs in promoting in cancer metastasis

Exosomal miRNAs	Originating cells	Receiving cells	Target	Note	Ref
miR-500a-5p (Up)	CAFs	Breast cancer	USP28	Exosomal miR-500a-5p derived from CAFs aggravates metastasis in breast cancer cells by targeting USP28	[49]
miR-18b (Up)	CAFs	Breast cancer	TCEAL7	Exosomal miR-18b derived from CAFs leads to the induction of breast cancer metastasis by targeting TCEAL7	[50]
miR-3613-3p (Up)	CAFs	Breast cancer	SOCS2	CAFs-derived exosomal miR-3613-3p promotes breast cancer metastasis by targeting SOCS2	[51]
miR-16 and miR-148a (Up)	CAFs	Breast cancer	-	Exosomal miR-16 and miR-148a derived from CAFs promotes breast cancer metastasis	[52]
miR-369 (Up)	CAFs	LSCC	NF1	CAFs-derived exosomal miR-369 enhances LSCC metastasis by activating MAPK pathway through targeting NF1	[53]
miR-1290 (Up)	CAFs	Prostate cancer	GSK3β	CAFs-derived exosomal miR-369 induces prostate cancer metastasis by enhancing EMT, migration, invasion and stemness through targeting GSK3β	[54]
miR-92a-3p (Up)	CAFs	CRC	FBXW7 and MOAP1	CAFs- secreted exosomal miR-92a-3p aggravates CRC cell metastasis by enhancing EMT and stemness through targeting FBXW7 and MOAP1	[55]
miR-193-3p, -210-3p and -5100	B-MSCs	Lung cancer	-	BMSCs-derived exosomal miR-193-3p, -210-3p and -5100 enhances lung cancer metastasis by inducing EMT through regulating STAT3	[56]
miR-425	B-MSCs	Lung cancer	CPEB1	BMSCs-derived exosomal miR-425 enhances lung cancer metastasis by inducing EMT, invasion and migration through negatively regulating CPEB1	[57]
miR-769-5p	B-MSCs	Osteosarcoma	DUSP16	Exosomal miR-769-5p derived from BMSC enhances osteosarcoma metastasis by negatively regulating DUSP16	[58]
miR-30a and miR-222	hCC-MSCs	Colon cancer	MIA3	Exosomal miR-30a and miR-222 secreted from MSCs originated from colon cancer stem cells induces colon cancer metastasis by targeting MIA3	[59]

Table 1 (continued)

Exosomal miRNAs	Originating cells	Receiving cells	Target	Note	Ref
miR-221-3p	M2-TAMs	Osteosarcoma	SOCS3	M2-TAMs-derived exosomal miR-221-3p enhances osteosarcoma metastasis by regulating SOCS3/JAK2/STAT3 axis through targeting SOCS3	[60]
miR-501-3p	M2-TAMs	Pancreatic ductal adenocarcinoma	TGFBR3	M2-TAMs-derived exosomal miR-501-3p enhances pancreatic ductal adenocarcinoma by promoting migration and invasion through targeting TGFBR3	[61]
miR-223-3p	TAMs	Breast cancer (4T1 cell)	Cbx5	TAMs-derived exosomal miR-223-3p enhances pulmonary metastasis of breast cancer cells by targeting Cbx5	[62]
miR-202-5p and miR-142-5p	TAMs	Pancreatic ductal adenocarcinoma	PTEN	TAMs-derived exosomal miR-202-5p and miR-142-5p can enhance pancreatic ductal adenocarcinoma metastasis by targeting PTEN	[63]
miR-155 and miR-196a-5p	TAM	Non-small-cell lung cancer	RASSF4	Exosomal miR-155 and miR-196a-5p enhances the non-small-cell lung cancer metastasis by negatively regulating RASSF4 levels	[64]
miR-21-5p	Pro-tumorigenic M2 macrophages	RCC	PTEN	Pro-tumorigenic M2 macrophages-derived exosomal miR-21-5p enhances RCC metastasis by targeting PTEN	[65]
miR-4299	Hypoxic CRC cells	CRC cell	ZBTB4	Hypoxic CRC cells-derived exosomal miR-4299 promotes CRC metastasis by targeting ZBTB4	[66]
miR-1273f	Hypoxic HCC cells	HCC	LHX6	Hypoxic HCC cells-derived exosomal miR-1273f enhances HCC metastasis by targeting LHX6	[67]
miR-301a-3p	Hypoxic TME of gastric cancer	Gastric cancer	PHD3	Hypoxic TME of gastric cancer-derived exosomal miR-301a-3p enhances gastric cancer metastasis and EMT by targeting PHD3	[68]
miR-301a-3p	Pancreatic cancer cells under hypoxic conditions	Pancreatic cancer cells	PTEN	Exosomal miR-301a-3p derived from pancreatic cancer cells under hypoxic conditions leads to the induction of pancreatic cancer cell metastasis by activating M2 macrophage polarization through targeting PTEN	[69]
miR-455	Hypoxic NPC cells	NPC	ZO-1	Hypoxic NPC cells-secreted exosomal miR-455 enhances NPC metastasis by targeting ZO-1	[70]

Table 1 (continued)

Exosomal miRNAs	Originating cells	Receiving cells	Target	Note	Ref
miR-625-3p	Hypoxic lung cancer cells	Lung cancer	SCAI	Hypoxic lung cancer cells-derived exosomal miR-625-3p enhances lung cancer metastasis by targeting SCAI	[71]
miR-619-5p	Hypoxic NSCLC cell	NSCLC	RCAN1.4	Hypoxic NSCLC cell-derived exosomal miR-619-5p promotes NSCLC metastasis potential to lateral tail veins of mice by inducing angiogenesis through targeting RCAN1.4	[72]
miR-31-5p	Hypoxic LUAD cell	LUAD	SATB2	Hypoxic LUAD cell-derived exosomal miR-31-5p enhances normoxic LUAD metastasis by promoting migration and invasion through targeting SATB2	[73]
miR-106b (Up)	EMT-CRC cells	CRC cells	PDCD4	Exosomal miR-106b derived from EMT-CRC cells enhances the macrophages polarization by targeting PDCD4. In return, activated macrophages leads to the promotion CRC cells metastasis by inducing EMT, invasion and migration	[74]
miR-335-5p	Metastatic CRC SW620 cell	CRC cell	RASA1	Exosomal miR-335-5p derived from metastatic CRC cells promotes CRC metastasis by enhancing EMT through targeting RASA1	[30]
miR-203a-3p	CRC cell	CRC	PTEN	CRC cell-derived exosomal miR-203a-3p induces CRC metastasis by promoting macrophage polarization through targeting PTEN	[75]
miR-934	CRC cell	Liver	PTEN	Exosomal miR-934 derived from CRC cells aggravates liver metastasis by promoting M2 macrophage polarization through targeting PTEN	[39]
miR-130b-3p, miR-425-5p, and miR-25-3p	CRC cell	Liver	PTEN	CRC cells-derived exosomal miR-130b-3p, miR-425-5p, and miR-25-3p promotes liver metastasis by enhancing M2 macrophage polarization through negatively regulating PTEN expression levels	[76]
miR-221/ 222	CRC cell	Liver	SPINT1	CRC cells-derived exosomal miR-221/ 222 enhances liver metastasis by targeting SPINT1	[36]

Table 1 (continued)

Exosomal miRNAs	Originating cells	Receiving cells	Target	Note	Ref
miR-25-3p (Up)	CRC	Liver and lung	KLF2, and KLF4	Exosomal miR-25-3p enhances CRC metastasis in liver and lung of mice by promoting pre-metastatic niche through targeting KLF2, and KLF4	[77]
miR-21-3p and miR-769-3p	CRC cell-mutant P53 (HCT116-TP53(R273H) cells)	Pulmonary metastasis	-	The mutant p53-derived exosomal miR-21-3p and miR-769-3p enhances pulmonary metastasis by activating stromal fibroblasts and premetastatic niche. In return, activated fibroblasts promotes tumor cell EMT by positively regulating TGF-β	[37]
miR-203a-3p	CRC cell	CRC cell	PTEN	CRC cell-derived exosomal miR-203a-3p enhances M2 macrophage polarization by targeting PTEN. In return, polarized macrophages promote CRC metastasis by secreting CXCL12	[75]
miR-29a	EMT-CRC	CRC (endothelial cells in the TME)	KLF4	Exosomal miR-29a derived from EMT-CRC enhances metastasis in endothelial cells in the tumor microenvironment by targeting KLF4	[33]
miR-106b-3p	High invasive potential CRC cells (KM12SM)	Low invasive potential CRC cell (SW480) and lung	DLC-1	Exosomal miR-106b-3p derived from high invasive potential CRC cells promotes metastasis by inducing EMT through targeting DLC-1	[31]
miR-146a-5p and miR-155-5p	CXCL12/ CXCR7-induced CRC cells	CRC and lung	ZBTB2 and SOCS1	Exosomal miR-146a-5p and miR-155-5p derived from CXCL12/CXCR7-induced CRC cells aggravates CAFs activation by targeting ZBTB2 and SOCS1. In return, activated CAFs enhances CRC and lung metastasis	[78]
miR-27b-3p	EMT-CRC	Blood vessel endothelium	VE-Cad and p120	EMT-CRC- secreted exosomal miR-27b-3p promotes metastasis by targeting VE-Cad and p120	[32]
miR-200b-3p	Breast cancer	Lung epithelial cells	PTEN	Exosomal miR-200b-3p derived from breast cancer cells induces metastasis in lung cells by promoting CCL2 release by targeting PTEN	[79]
miR-10b (Up)	Metastatic breast cancer	Non-invasive breast epithelial HMLE cells	HOXD10	Exosomal miR-10b derived from metastatic breast cancer leads to induction of metastasis by inducing invasion in non-invasive breast epithelial HMLE cells through targeting HOXD10	[80]

Table 1 (continued)

Exosomal miRNAs	Originating cells	Receiving cells	Target	Note	Ref
miR-222 (Up)	Breast cancer	Breast cancer	PDLIM2	Exosomal miR-222 enhances breast cancer metastasis by inducing invasion and migration through targeting PDLIM2	[81]
miR-146a (Up)	Breast cancer	Breast cancer	TXNIP	Exosomal miR-146a derived from breast cancer cells promotes metastasis by activating CAFs through inducing Wnt pathway and targeting TXNIP	[82]
miR-9 and miR-155	High-metastatic breast cancer cells	Low-metastatic breast cancer cells	PTEN and DUSP14	High-metastatic breast cancer cells-secreted exosomal miR-9 and miR-155 can enhance the metastasis in low-metastatic breast cancer cells by targeting PTEN and DUSP14	[83]
miR-1246	Metastatic breast cancer cells	Non-metastatic breast cancer cells	CCNG2	Exosomal miR-1246 secreted from metastatic breast cancer cells promotes metastasis by inducing invasion through targeting CCNG2	[84]
miR-503	Breast cancer	Brain cancer	-	Released exosomal miR-29a-3p from breast cancer mediated with downregulation XIST aggregates brain metastasis by promoting microglia polarization from M1 to M2, and activating microglia	[85]
miR-19a	ER + breast cancer	Bone metastasis	PTEN	ER + breast cancer-derived exosomal miR-19a enhances bone metastasis by inducing osteoclastogenesis through targeting PTEN	[86]
miR-1910-3p	Breast cancer cells	Breast cancer cells	MTMR3	Breast cancer cells-derived exosomal miR-1910-3p promotes metastasis by inducing migration through targeting MTMR3	[87]
miR-4443	Highly invasive breast cancer cells	Liver	-	Highly invasive breast cancer cells-derived exosomal miR-4443 promotes liver metastasis maybe by targeting TIMP2	[88]
miR-193b	Breast cancer cell (SK-BR-3 cells)	Breast cancer	RAB22A	Exosomal miR-193b suppresses breast cancer metastasis by targeting RAB22A	[89]
miR-210-3p	Lung cancer stem cells	Lung cancer	FGFRL1	Lung cancer stem cells-derived exosomal miR-210-3p enhances lung cancer metastasis by targeting FGFRL1	[90]

Table 1 (continued)

Exosomal miRNAs	Originating cells	Receiving cells	Target	Note	Ref
miR-21	Lung cancer tumorspheres	Brain cancer	DGKB	Lung cancer tumorspheres-exosomal miR-21 promotes brain metastasis by inducing EMT and activating ERK/STAT3 signaling pathway through targeting DGKB	[91]
miR-106b (Up)	Lung cancer	Lung cancer	PTEN	Exosomal miR-103 derived from lung cancer cell enhances lung cancer metastasis by positively regulating MMP-2 and MMP-9 and by targeting PTEN	[92]
miR-499a-5p	Highly metastatic lung cancer cell	Lung adenocarcinoma	-	Highly metastatic lung cancer cell-secreted exosomal miR-499a-5p enhances lung adenocarcinoma metastasis by promoting EMT, and migration through regulating mTOR pathway	[93]
miR-375-3p	SCLC	SCLC	Claudin-1	SCLC-derived exosomal miR-375-3p enhances metastasis by promoting transendothelial migration by negatively regulating claudin-1 levels	[94]
miR-1260b	NSCLC	NSCLC	HIPK2	NSCLC-derived exosomal miR-1260b promotes NSCLC metastasis by inducing invasion and migration through targeting HIPK2	[95]
miR-3157-3p	NSCLC	HUVEC	TIMP2 and KLF2	NSCLC-secreted exosomal miR-3157-3p enhances metastasis by inducing angiogenesis and vascular permeability through targeting TIMP2 and KLF2	[96]
miR-19b-3p	Lung adenocarcinoma (LUAD)	LUAD	PTPRD	Lung adenocarcinoma-derived exosomal miR-19b-3p enhances M2 macrophages polarization and secretion exosomal LINC00273 by targeting PTPRD. In return, exosomal LINC00273 enhances the metastasis of LUAD	[97]
miR-197-3p	LUAD	HUVEC	TIMP2/3	LUAD cells-derived exosomal miR-197-3p enhances LUAD metastasis by inducing angiogenesis through targeting TIMP2/3	[98]
miR-133a-3p	Lung cancer	Lung cancer	SIRT1	Exosomal miR-133a-3p secreted from lung cancer cells following incomplete microwave ablation enhances lung cancer metastasis by targeting SIRT1	[99]

Table 1 (continued)

Exosomal miRNAs	Originating cells	Receiving cells	Target	Note	Ref
miR-103 (Up)	Hepatoma cell	Endothelial cells (liver and lung metastasis)	VE-Cad, p120 and ZO-1	Exosomal miR-103 derived from hepatoma cell promotes liver metastasis by regulating VE-Cad, p120 and ZO-1	[92]
miR-29a-3p	High-metastatic HCC cells	Low-metastatic HCC cells	PTEN	Exosomal miR-29a-3p derived from high-metastatic HCC cells promotes HCC metastasis by enhancing EMT in low-metastatic HCC cells by targeting PTEN	[100]
miR-21 and miR-10b	HCC cells cultured under acidic condition	HCC	-	HCC cells cultured under acidic condition-derived exosomal miR-21 and miR-10b promotes HCC metastasis	[101]
miR-574-5p	Liver cancer	Bone metastasis	BMP2	Liver cancer-derived exsosomal miR-574-5p enhances bone metastasis by promoting osteoclastogenesis through targeting BMP2	[102]
miR-1247-3p	HCC	Lung cancer	B4GALT3	Exosomal miR-1247-3p derived from high-metastatic HCC cells leads to converting fibroblasts to CAFs by negatively regulating B4GALT3. In return, CAFs enhance lung metastasis by promoting EMT and stemness	[103]
miR-486-5p	Gastric cancer	Gastric cancer	ACTR3	Exosomal miR-486-5p derived from gastric cancer cells enhances peritoneal metastasis of gastric cancer by inducing EMT through targeting ACTR3	[104]
miR-196a-1	High-invasive GC cells	Liver and low-invasive GC cells	SFRP1	High-invasive GC cells-derived exosomal miR-196a-1 enhances the metastasis of liver and low-invasive GC cells by targeting SFRP1	[105]
miR-423-5p (Up)	Gastric cancer	Gastric cancer	SUFU	Exosomal miR-423-5p derived from gastric cancer cells promotes metastasis by targeting SUFU	[106]
miR-21-5p	Gastric cancer	Peritoneal metastasis	SMAD7	Gastric cancer-derived exosomal miR-21-5p enhances peritoneal metastasis by promoting EMT through targeting SMAD7	[107]

Table 1 (continued)

Exosomal miRNAs	Originating cells	Receiving cells	Target	Note	Ref
miR-519a-3p	Gastric cancer	Liver	DUSP2	Gastric cancer-derived exosomal miR-519a-3p enhances the macrophages polarization by targeting DUSP2. In return, activated macrophages leads to the promotion liver cells metastasis by inducing angiogenesis	[108]
miR-106a	Gastric cancer	Peritoneal	Smad7	Gastric cancer-derived exosomal miR-106a promotes peritoneal metastasis by negatively regulating the expression level of miR-106a	[109]
miR-1246	Highly metastatic human oral cancer cell line (HOC313-LM)	OSCC	DENND2D	Highly metastatic human oral cancer-derived exosomal miR-1246 promotes OSCC metastasis by increasing migration and invasion through targeting DENND2D	[110]
miR-23b-3p	Salivary adenoid cystic carcinoma	Salivary adenoid cystic carcinoma	PTEN	Salivary adenoid cystic carcinoma cell-derived exosomal miR-23b-3p promotes SACC metastasis by aggravates angiogenesis through targeting PTEN	[111]
miR-205-5p	NPC	HUVECs and NPC	DSC2	Exosomal miR-205-5p promotes HUVECs' angiogenesis to aggravate distant metastasis of NPC by targeting DSC2	[112]
miR-18a-5p	NPC	NPC	BTG3	NPC cells-derived exosomal miR-18a-5p enhances NPC metastasis by inducing EMR, migration and invasion through targeting BTG3	[112]
miR-620	ESCC	ESCC	FOXM1/ HER2	ESCC-derived exosomal miR-620 enhances ESCC metastasis by activating aerobic glycolysis in lung fibroblasts through targeting FOXM1/HER2	[113]
miR-320b	ESCC	HLECs	PDCD4	ESCC-derived exosomal miR-320b induces the metastasis of human lymphatic endothelial cells (HLECs) by promoting EMT through targeting PDCD4	[114]
miR-21	Esophageal carcinomas cell line (EC9706)	Esophageal cancer	PDCD4	EC9706 cell-derived exosomal miR-21 induces esophageal cancer metastasis by promoting migration and invasion through targeting PDCD4	[115]

Table 1 (continued)

Exosomal miRNAs	Originating cells	Receiving cells	Target	Note	Ref
miR-141-3p	Prostate cancer	Osteoblastic	DLC1	Prostate cancer cells-derived exosomal miR-141-3p induces osteoblastic metastasis by negatively regulating DLC1	[116]
miR-375	Prostate cancer	Osteoblastic	DIP2C	Prostate cancer cells-derived exosomal miR- miR-375 induces osteoblastic metastasis by activating Wnt signaling pathway through targeting DIP2C	[117]
miR-183	Prostate cancer cell (PC3 cells)	Prostate cancer (LNCaP cell)	TPM1	PC3 cells-derived exosomal miR-183 promotes prostate cancer cell (LNCaP cell) metastasis by inducing invasion and migration through targeting TPM1	[118]
miR-199a-1-5p	High-metastatic melanoma cells	Low-metastatic melanoma cells	CDKN1B	High-metastatic melanoma cells-derived exosomal miR-199a-1-5p enhances the metastasis of low-metastatic melanoma cells by targeting CDKN1B	[119]
miR-411-5p	High-metastatic melanoma cells	Low-metastatic melanoma cells	-	Exosomal miR-411-5p derived from high-metastatic melanoma cells-derived can promote the metastasis of low-metastatic melanoma cells	[120]
miR-4535	Melanoma stem cells	Melanoma parental cells	-	Exosomal miR-4535 derived from melanoma stem cells enhances metastasis of melanoma parental cells by inhibiting autophagy	[121]
miR-125b-5p	Highly invasive pancreatic cancer cells	Weakly invasive pancreatic cancer cells	STARD13	Highly invasive pancreatic cancer cells-derived exosomal miR-125b-5p promotes the metastasis of weakly invasive pancreatic cancer cells by enhancing EMT through targeting STARD13	[122]
miR-3960	Pancreatic cancer (PANC-1 cell)	Pancreatic cancer	TFAP2A	Pancreatic cancer-derived exosomal miR-3960 promotes metastasis by targeting TFAP2A	[123]
miR-126a	MDSCs treated with doxorubicin	Lung cancer	-	Exosomal miR-126a derived from myeloidderived suppressor cells (MDSCs) treated with doxorubicin enhances lung cancer metastasis	[124]
miR-205	Ovarian cancer	Cancer-adjacent endothelial cells	PTEN	Ovarian cancer-derived exosomal miR-205 enhances the metastasis by inducing angiogenesis through targeting PTEN	[125]

Table 1 (continued)

Exosomal miRNAs	Originating cells	Receiving cells	Target	Note	Ref
miR-141	Ovarian cancer	Ovarian cancer	YAP1	Ovarian cancer-derived exosomal miR-141 enhances metastasis by positively regulating GROα through targeting YAP1. In return, upregulated GROα promotes metastasis by inducing migration, invasion and colonization of ovarian cancer cells	[126]
miR-663b	Cervical cancer	Cervical cancer	MGAT3	Exosomal miR-663b derived from TGF-β1-treated cervical cancer cells promoting cervical cancer metastasis by inducing EMT and migration through targeting MGAT3	[127]
miR-221-3p	Cervical squamous cell carcinoma	Lymphatic metastasis	VASH1	Exosomal miR-221-3p derived from cervical squamous cell carcinoma enhances lymphatic metastasis through targeting VASH1	[128]
miR-148a	Glioma cells	Glioblastoma	CADM1	Glioma cells-derived exosomal miR-148a enhances glioblastoma metastasis by targeting CADM1	[129]
miR-675 (Up)	Metastatic OS	Non-malignant fibroblast cells (hFOB1.19)	CALN1	Exosomal miR-675 derived from Metastatic OS cells promotes invasion and migration of non-malignant fibroblast cells by negatively regulating CALN1 levels	[130]
miR-421	Adipose microenvironment	Ovarian cancer	CBX7	Adipose microenvironment-derived exosomal miR-421 enhances ovarian cancer metastasis by targeting CBX7	[131]
miR-6780b-5p	Ascites-derived exosomes	Ovarian cancer	-	Ascites-derived exosomal miR-6780b-5p enhances ovarian cancer metastasis by promoting EMT	[132]
miR-4466	Nicotine-activated neutrophils	Lung cancer	-	Exosomal miR-4466 derived from nicotine-activated neutrophils enhances lung cancer metastasis	[133]

Table 2 Role of Exosomal miRNAs in inhibiting in cancer metastasis

Exosomal miRNAs	Originating cells	Receiving cells	Target	Note	Ref
miR-29c-3p (Down)	Omental-CAFs	Ovarian cancer peritoneal	MMP2	Omental-CAFs-derived exosome with low miR-29c-3p enhances ovarian cancer peritoneal metastasis by targeting MMP2	[134]
miR-320a (Down)	CAFs	HCC	PBX3	Downregulated exosomal miR-320a derived from CAFs leads to inducing HCC metastasis by upregulating PBX3	[135]
miR-34a-5p	CAFs	OSCC	AXL	CAFs-derived exosomal m miR-34a-5p inhibits OSCC metastasis by reducing EMT and MMP through targeting AXL	[136]
miR-148b (Down)	CAFs	Endometrial cancer	DNMT1	Exosomal miR-148b inhibits endometrial cancer metastasis by alleviates EMT, and invasion through targeting DNMT1	[137]
miR-146a-5p (Down)	CAFs	Prostate cancer	EGFR	DHT-treated CAFs-derived exosomal miR-146a-5p inhibits prostate cancer metastasis by inhibiting EMT, invasion and migration by targeting EGFR	[138]
miR-319	CAFs	Gastric cancer	MMP11	Gastric CAFs-derived exosomal miR-319 inhibits gastric cancer metastasis by negatively regulating MMP11 levels	[139]
miR-3940-5p	MSC	CRC	ITGA6	MSC-derived exosomal miR-3940-5p suppresses CRC metastasis by inhibiting invasion and EMT through ITGA6	[140]
miR-23b	BM-MSC	Breast cancer cell (BM2)	MARCKS	BM-MSC-derived exosomal miR-23b aggravates the dormancy of breast cancer in the metastatic niche	[141]
miR-100 and miR-143	MSCs	CRC	-	MSCs-derived exosomal miR-100 and miR-143 inhibits CRC metastasis maybe by targeting mTOR	[142]
miR-499a-5p	MSCs	Endometrial cancer	VAV3	MSC-derived exosomal miR-499a-5p inhibits endometrial cancer metastasis by inhibiting angiogenesis through targeting VAV3	[143]
miR-342-3p	MSCs	Breast cancer	ID4	MSC-derived exosomal miR-342-3p suppresses breast cancer metastasis by inhibiting invasion through targeting ID4	[144]
miR-128	MSCs	Urothelial carcinoma	CCL18	MSC-derived exosomal miR-128 suppresses urothelial carcinoma metastasis by inhibiting migration and invasion through targeting CCL18	[145]
miR-320a	Umbilical cord mesenchymal stem cells	Lung cancer	SOX4	Umbilical cord MSCs-derived exosomal miR-320a inhibits lung cancer metastasis by targeting SOX4	[146]
miR-199a-5p	Hypoxic Ovarian cancer	Ovarian cancer	HIF-2α	Hypoxic ovarian cancer cell-derived eoxosmal miR-199a-5p inhibits ovarian cancer metastasis by targeting HIF-2α	[147]
miR-363-5p	Breast cancer	Breast cancer cell (MCF-7)	PDGFB	Exosomal miR-363-5p inhibits breast cancer cell metastasis by inhibiting migration and invasion through targeting PDGFB	[148]

Table 2 (continued)

Exosomal miRNAs	Originating cells	Receiving cells	Target	Note	Ref
miR-122-3p	Breast cancer (MCF-7)	Breast cancer (MCF-7/ADR cells)	GRK4	Breast cancer-derived exosomal miR-122-3p suppresses metastasis by inhibiting Wnt/β-catenin signaling pathway through targeting GRK4	[149]
miR-550a-3-5p	Lung cancer	Brain	YAP1	Lung cancer-derived exosomal miR-550a-3-5p can control brain metastasis by targeting YAP1	[150]
Let-7e	Serum-derived exosomes NSCLC patients	NSCLC (H1299 cells)	SUV39H2	Exosomal let-7a derived from serum of NSCLC patients suppresses invasion and migration of NSCLC by targeting SUV39H2	[151]
miR-338-3p	Human normal lung epithelial cells (BEAS-2B)	NSCLC	CHL1	Human normal lung epithelial cells (BEAS-2B)-derived exosomal miR-338-3p inhibits NSCLC metastasis by targeting CHL1	[152]
miR-3180-3p (Down)	Human bronchial epithelial cells	NSCLC	FOXP4	Exosomal miR-3180-3p inhibits NSCLC metastasis by targeting FOXP4	[153]
miR-125b	Non-metastatic HCC	HCC	SMAD2	Exosomal miR-125b inhibits HCC metastasis by inhibiting EMT through targeting SMAD2	[154]
miR-10527-5p	ESCC	HLECs and ESCC	Rab10	ESCC-derived exosomal miR-10527-5p can inhibit ESCC metastasis by suppressing EMT, migration and invasion through negatively regulating Rab10/ Wnt/β-Catenin Signaling	[155]
miR-485-3p	Pancreatic ductal epithelial cells	Pancreatic cancer	PAK1	Pancreatic ductal epithelial cells-derived exosomal miR-485-3p suppresses pancreatic cancer metastasis by targeting PAK1	[156]
miR-7	TWEAK-stimulated macrophages	Epithelial ovarian cancer	-	Exosomal miR-7 derived from TWEAK-stimulated macrophages inhibits the metastasis of epithelial ovarian cancer cells by regulating EGFR/AKT/ERK1/2 pathway	[157]
miR-490	Mast cells (MCs)	HCC	-	Mast cells (MCs)-derived exosomal miR-490 inhibits HCC metastasis by inhibiting invasion and migration by regulating EGFR/AKT/ERK1/2 pathway	[158]

a worse prognosis in TNBCs. MiR-105 was characteristically secreted by memory B cell (MBC) and was a potent migration regulator through targeting the tight junction protein zona occluden-1 (ZO-1) [164]. In endothelial monolayers, exosomal miR-105 secreted by BC cells disrupts the integrity of natural barriers and favors metastasis. Clinically, miR-105 have been detected in the circulation at the pre-metastatic stage, and its levels in the blood and tumor were associated with ZO-1 expression and metastasis in early-stage BC. Prior to neoadjuvant therapy, a comparative analysis of exosomal miRNA expression levels revealed significantly elevated levels of miR-21 and miR-105 in patients with metastatic breast cancer compared to those with non-metastatic disease and healthy donors [165].

MiR-155 is an oncogenic miRNA which its upregulation is commonly detected in BC and is implicated in the recurrence, metastasis, and resistance. MiR-155 is found to be abundant in cancer stem cells (CSCs) and resistant cells, and can be transmitted to BC cells through exosomes [166]. It has been demonstrated that exosomes can modify the migratory potential and enhance EMT in sensitive cells, partly through exosomal transfer of miR-155. A study by Gorczynski et al. found that both miR-155 and miR-205 play a crucial role in modulating

the inflammatory response, thereby influencing the metastatic growth of BC cells in lung and liver metastasis models. Notably, elevated levels of BC exosomal miR-205 have been shown to suppress BC metastasis, whereas miR-155 has been found to have an opposite effect [167]. Through a bioinformatic analysis, Kia et al. identified that miR-9 and miR-155 were among the most highly expressed miRNAs in highly metastatic TNBC cells and their corresponding exosomes. This finding was subsequently validated through qRT-PCR experiments, providing further evidence for the potential role of these miRNAs in the biology of TNBC metastasis [83]. A luciferase assay confirmed that the miR-9 and miR-155, which were present in the exosomes of BC cells, specifically targeted the UTRs of PTEN and DUSP14 genes, respectively. In a subsequent study, when low-metastatic MCF-7 cells were treated with exosomes from highly metastatic MDA-MB-231 cells, they exhibited an enhanced metastatic phenotype, suggesting that the transfer of these exosomal miRNAs can modulate the migratory behavior of recipient cells [168]. The study revealed that the miR-155 shuttled by exosomes introduced a novel mechanism that promoted the development and metastasis of cancer. Furthermore, the researchers found that the levels of miR-7641 were elevated in the exosomes derived from BC cells and were also present in the plasma of breast cancer patients with distant metastases. Notably, this miR-7641 was found to stimulate tumor growth both in vitro and in vivo, suggesting a potential role for this miRNA in the progression of BC [169]. The study demonstrated that the miR-7641, secreted through exosomes, can promote the proliferation and invasion of BC cells. Additionally, miR-7641 can also induce epigenetic changes in recipient cells through exosome-mediated transfer. Similarly, another study found that the exosomal miR-1246, secreted from metastatic BC cells, plays a crucial role in promoting metastasis by inducing invasion in non-metastatic BC cells. Specifically, miR-1246 was shown to target the *CCNG2* gene, leading to enhanced invasion capabilities in recipient cells. These findings suggest that exosomal miRNAs may play a significant role in modulating the behavior of BC cells and potentially contributing to disease progression [84].

In selective metastasis, tumor-derived exosomal miRNAs exhibit abnormal expression and play a key role in preparing the pre-metastatic niche by reprogramming the target organ, enhancing the likelihood of successful metastasis [14]. For instance, the expression of exosomal miR-19a and integrin-binding sialoprotein (IBSP) is significantly upregulated in the secretion of estrogen receptor-positive (ER+) bone-tropic breast cancer cell lines, as well as in ER+breast cancer patients with bone metastases [86]. Additionally, Wu and colleagues [86] has identified that exosomal miR-19a derived from ER+breast cancer cells enhances bone metastasis by promoting osteoclastogenesis through the targeting of PTEN. In the early metastatic niche, ER+breast cancer cells secrete integrin-binding sialoprotein (IBSP) as a chemoattractant, recruiting precursors of osteoclast (OC) cells and creating an OC precursor-enriched microenvironment. These OC precursors subsequently internalize exosomes from breast cancer cells, allowing miR-19a to be transported into the OC precursors, where it exerts its pro-tumorigenic effects [86]. Within the OC precursors, the internalized miR-19a suppresses the expression of phosphatase and tensin homolog (PTEN), activates the nuclear factor kappa B (NF-κB) and protein kinase B (AKT) signaling pathways, and promotes osteoclastogenesis. The resulting mature OC cells subsequently induce bone resorption, releasing growth factors from the bone matrix, which in turn facilitates the proliferation and survival of cancer cells [86]. Recently, Singh et al. [80] observed that miR-10b is significantly overexpressed in metastatic breast cancer cells compared to non-metastatic breast and non-malignant breast cells. Furthermore, upon internalization, miR-10b has been found to suppress the protein levels of its target genes, including homeobox D10 (HOXD10) and Krüppel-like factor 4 (KLF4), indicating its functional significance. Moreover, treatment with exosomes derived from metastatic breast cancer cells has been shown to induce metastasis by inducing invasive behavior in non-invasive breast epithelial HMLE cells through the targeting of HOXD10 [80]. More studies are shown in Tables 1 and 2.

Altogether, exosomal miRNAs have been identified as key mediators of selective metastasis, regulating gene expression, inducing EMT, and suppressing the immune response. These findings highlight the potential therapeutic significance of exosomal miRNAs as targets for the treatment of breast cancer.

Lung cancer

The majority of lung carcinomas are initially diagnosed at an advanced stage IV, often with widespread metastatic disease. Notably, lung carcinomas exhibit a propensity for metastasis via both lymphatic and hematogenous routes, reflecting their ability to spread through lymphatic vessels and the bloodstream [170]. The most common sites of metastasis for lung cancer are proposed to be the central nervous system, bone, liver, respiratory tract, and adrenal glands (Fig. 3) [171]. Recent studies have identified that certain exosomal miRNAs play a pivotal role in promoting lung cancer cell migration, invasion, tumor growth, and metastasis through multiple mechanisms [172, 173]. Notably, the dysregulation of these miRNAs

can be targeted to counteract their oncogenic effects, such as through gene silencing strategies. Runx3 (Runt-related transcription factor 3) has been found to be downregulated in lung cancer tissues, and it is considered a tumor suppressor due to its ability to antagonize the activation of the Wnt signaling pathway [174]. Exosomes derived from non-small cell lung cancer (NSCLC) cells, which contain miR-210 (miR-210-Exo), have been shown to modulate the behavior of recipient lung cancer cells by inhibiting Runx3 expression and activating the PI3K/Akt signaling pathway. This results in enhanced proliferation, migration, and invasion of the recipient cells [175]. In vivo, exosomal miR-210 was found to target the Runx3/PI3K/Akt axis, thereby promoting the growth of transplanted tumors in nude mice. Consistently, silencing of miR-210 gene expression significantly attenuated the carcinogenic effect induced by exosomal miR-210, underscoring the potential therapeutic relevance of targeting this axis in cancer treatment [175].

Epitopic overexpression of miRNA-30a-5p in lung cancer cells was found to significantly inhibit cell proliferation, migration, and invasion by targeting the cell-cycle phase regulator cyclin E2. Notably, miR-30a-5p-containing exosomes produced by vascular endothelial cells from lung adenocarcinoma (LUAD) patients were also found to effectively suppress cell proliferation, migration, and invasion, highlighting the potential therapeutic utility of miR-30a-5p-Exo in LUAD treatment [176]. HEY-like protein (HEYL) is a member of the hairy and enhancer of the split-related (HESR) family, and functions as a downstream target molecule of the Notch signaling pathway. This pathway has been implicated in the regulation of cell growth and metastasis in lung cancer (LC), suggesting that HEYL may also play a role in these processes [177, 178].

A comparison of exosomes derived from benign pleural effusion (BPE) and malignant pleural effusion (MPE) in lung cancer (LC) patients revealed that the level of miR-665 is significantly higher in MPE-derived exosomes [179]. Both cultured cells and experiments in zebrafish have confirmed that exosomes enriched with lncRNA SCIRT and miR-665 can enhance the migratory and invasive abilities of lung cancer cells by specifically targeting and suppressing HEYL. Furthermore, these findings indicated that the plasma concentrations of miR-665 and lncRNA SCIRT are significantly elevated in patients with metastatic lung cancer compared to those with non-cancerous diseases or non-metastatic lung cancer, suggesting that these exosomal biomarkers may serve as valuable indicators for the diagnosis and monitoring of metastatic disease [179]. Therefore, exosomal miR-665 in serum or lung pleural effusion may serve as a specific marker for the early diagnosis of lung cancer metastasis. Additionally, FOXP4, a member of the human forkhead-box (FOX) family, has been found to play a key role in cell cycle regulation and tumorigenesis. Notably, it has been established that FOXP4 protein and mRNA levels are significantly elevated in NSCLCs compared to normal lung tissue, indicating that FOXP4 may be a potential biomarker for LC diagnosis [180]. Chen and colleagues demonstrated that exosomal miR-3180-3p derived from NSCLC cells can exert anti-tumor effects by suppressing cell proliferation, migration, and invasion in recipient NSCLC cells through the downregulation of FOXP4 expression. Furthermore, the in vivo administration of miR-3180-3p-exosomes was shown to impede the growth and metastatic potential of NSCLC xenografts in nude mice [153].

The androgen receptor (AR) is a member of the steroid hormone receptor family and acts as a nuclear transcription factor. When bound to a ligand, AR undergoes a conformational change, allowing it to translocate to the nucleus, where it regulates the transcription of genes responsive to AR signaling. Notably, male NSCLC patients who exhibit androgen pathway manipulation (APM) have been found to have a survival advantage, suggesting a potential therapeutic benefit from targeting the androgen axis in this patient population [181]. Female NSCLC patients who have higher levels of (AR) expression have a substantially better overall survival compared to those without AR expression [182]. This suggests that the relationship between steroid hormones and their receptors in lung cancer patient survival is complex and warrants further investigation. Recent research by Zhou and colleagues has made progress in this area, revealing that miR-224-5p is overexpressed in cancer tissues from NSCLC patients and cell lines. Additionally, the study found that miR-224-5p, specifically in the form of extracellular vesicle-derived miR-224-5p, is produced by lung cancer cells and exerts oncogenic effects, promoting metastasis and cell proliferation in both NSCLC cells and normal human lung cells. These findings suggest a potential role for miR-224-5p in the progression of lung cancer, highlighting the need for further research to elucidate the underlying mechanisms [183]. The study also demonstrated that the overexpression of miR-224-5p in NSCLC cells led to a suppression of AR expression. This repression of AR had a profound impact on the behavior of the cancer cells, as it promoted EMT, proliferation, migration, invasion, and resistance to apoptosis. Furthermore, this overexpression also drove the growth of lung cancer xenografts. Conversely, silencing the AR gene in NSCLC cells enhanced their migratory potential and increased their resistance to apoptosis. These findings suggest that miR-224-5p plays a key role in regulating the progression of lung cancer by targeting the AR pathway, which

may have important implications for the development of novel therapeutic strategies [183]. This suggests that miR-224-5p-Exo can promote NSCLC progression by directly targeting AR. More studies are shown in Table 2.

Overall, these studies suggests that exosomal miRNAs play a pivotal role in the selective metastasis of lung cancer by facilitating the colonization of specific organs. Once internalized, these exosomal miRNAs reprogram recipient cells to promote their own proliferation, migration, and invasion, thereby creating a conducive microenvironment for metastatic lesion establishment. The targeting of specific organs by exosomal miRNAs is influenced by the expression profile of specific receptors or ligands on recipient cell surfaces, allowing lung cancer cells to selectively colonize particular organs and tissues. These findings underscore the significance of exosomal miRNAs in mediating selective metastasis in lung cancer and imply potential therapeutic strategies aimed at targeting these molecules to prevent or treat this disease.

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is a prevalent cancer type, ranking sixth in terms of incidence and third in terms of mortality globally. Notably, lung metastasis is the most frequent extrhepatic manifestation of HCC, underscoring the importance of understanding the mechanisms underlying this phenomenon [184]. In addition, bone metastases (BM) are a common phenomenon in patients with metastatic HCC, affecting 2–25% of cases. The presence of BM is often associated with a poor prognosis in HCC, highlighting the need for more effective diagnostic and therapeutic strategies to address this complication [185]. It has been demonstrated that exosomal miRNAs derived from HCC cells can play a significant role in promoting lung and bone metastasis. For instance, liver cancer-derived exosomal miR-574-5p has been shown to exacerbate bone metastasis by enhancing osteoclastogenesis through direct targeting of the BMP2 gene [102]. Furthermore, exosomal miR-1247-3p derived from high-metastatic HCC cells has been found to contribute to the conversion of fibroblasts to cancer-associated fibroblasts (CAFs) by directly targeting the B4GALT3 gene. In turn, CAFs have been shown to enhance lung metastasis by promoting EMT and stemness, indicating a critical role for exosomal miRNAs in the crosstalk between cancer cells and stromal cells during metastatic progression [103].

Exosomes released by HCC cells have also been found to influence the metastatic behavior of tumor cells. Research suggests that exosomal miR-21 and exosomal miR-10b, which are induced by acidic microenvironments, promote the proliferation and metastasis of cancer cells. As such, these exosomal miRNAs may serve as potential prognostic molecular markers and therapeutic targets for HCC [101]. In addition, exosomal miR-125b has been found to exert anti-tumor effects by inhibiting the metastasis of HCC cells. Specifically, exosomal miR-125b has been shown to suppress EMT by targeting the SMAD2 gene, which is a key regulator of EMT [154]. Interestingly, exosomal miR-29a-3p released by high-metastatic HCC cells has been found to promote metastasis by enhancing EMT in low-metastatic HCC cells. This pro-metastatic effect is mediated by exosomal miR-29a-3p targeting the phosphatase and tensin homolog (PTEN) gene, a key regulator of EMT. This finding suggests that exosomal miR-29a-3p may act as a "metastatic bridge" between high-metastatic and low-metastatic HCC cells, promoting the dissemination of cancer cells through EMT activation [100].

Blood-borne metastasis, which refers to the spread of cancer cells through the bloodstream, is the primary cause of mortality in patients with cancer. The process of metastasis is facilitated by increased vascular permeability, which allows cancer cells to extravasate from the bloodstream and colonize distant organs. This highlights the critical role of the vasculature in promoting tumor dissemination and underscores the importance of understanding the molecular mechanisms underlying vascular permeability in cancer progression. Furthermore, targeting these mechanisms may provide a promising therapeutic strategy for inhibiting metastasis and improving patient outcomes [186]. A study by Fang et al. [92] demonstrated that exosomes secreted by HCC cells can transfer miR-103 to endothelial cells, thereby inhibiting the expression of key proteins involved in endothelial tight junction integrity, such as human vascular endothelial cadherin, zonula occludens 1, and p120-catenin. This led to a weakening of endothelial connectivity, increased vascular permeability, and accelerated metastasis. In a xenograft mouse model, high miR-103 expression was associated with an increased probability of intrahepatic and pulmonary metastasis. Notably, HCC patients with elevated serum miR-103 levels exhibited a higher metastatic potential compared to those with low miR-103 expression levels. These findings collectively suggest a positive correlation between exosomal miR-103 expression and the metastatic capacity of HCC [92, 187].

The mitogen-activated protein kinases (MAPKs) constitute a family of evolutionarily conserved serine/threonine protein kinases that play crucial roles in various cellular processes, including cell proliferation, differentiation, motility, and apoptosis [188]. The MAPK family, comprising p44/42 (ERK1/2), p46/p54 (JNK), and p38, serves as a critical component of protein kinase cascades, which are essential for regulating cell growth and differentiation, as well as modulating cellular responses

to cytokines and stress signals [189]. The p44/42 MAPK (ERK1/2) signal transduction pathway is activated in response to a diverse range of extracellular stimuli, including mitogens, growth factors, and cytokines [190, 191], and it is an important target for cancer diagnosis and treatment [192]. Recent studies have demonstrated that exosomal miR-320a exhibits anti-tumor effects on HCC cells by suppressing cell proliferation, migration, and metastasis through the inhibition of the MAPK pathway, which ultimately leads to the induction of EMT and the upregulation of cyclin-dependent kinase 2 (CDK2) and matrix metallopeptidase 2 (MMP2) expression [135]. In the study conducted by Li Xiong et al., mast cells have been shown to inhibit the ERK1/2 pathway by delivering exosomal miR-490 to HCC cells, thereby suppressing the metastatic potential of HCC cells [158]. Activation of MAPK signaling pathway is a frequently observed event in the progression and metastasis of tumors, highlighting its significance as a potential therapeutic target for cancer treatment [193, 194]. These studies can provide new insights into the regulatory mechanism of HCC in the MAPK signaling pathway and identify potential ways of the therapeutic intervention for the disease.

Overall, these findings highlight the potential for exosomal miRNAs to serve as key mediators of metastatic spread in HCC, and underscores the importance of further investigating their mechanisms of actions.

Head and neck cancer

Head and neck cancer (HNC) is a prevalent and debilitating neoplasm globally, with a significant burden on public health. Despite ongoing advances in therapeutic modalities, the 5-year overall survival rate for advanced HNC remains disappointingly low, hovering around 50%, underscoring the pressing need for innovative treatment strategies to improve patient outcomes [195–198]. HNC often originates from mucosal surfaces, specifically the oral cavity, which includes the tongue, lip, buccal mucosa, gingiva, and palate, as well as the oropharynx, larynx, and perioral skin, highlighting the importance of early detection and surveillance in these high-risk areas [199]. The majority of HNCs, exceeding 90%, are classified as head and neck squamous cell carcinomas (HNSCCs). Recent studies have uncovered a wealth of evidence indicating that tumor-derived exosomal miRNAs play a pivotal role in the oncogenic process, facilitating intercellular communication and signal transduction pathways that contribute to tumor development, progression, and treatment resistance [200, 201]. For instance, research has demonstrated that exosomes secreted by hypoxic oral squamous cell carcinoma (OSCC) cells transfer viral miR-21 to normoxic cells, inducing EMT and subsequently promoting cell migration and invasion [202]. Notably, research has shown that exosomal miR-21 derived from esophageal carcinoma cell line EC9706 promotes metastasis in esophageal cancer by enhancing migration and invasion through targeting the protein programmed cell death 4 (PDCD4) [115]. It has been demonstrated that miR-23b-3p derived from salivary adenoid cystic carcinoma (SACC) cells and packaged in exosomes can contribute to SACC metastasis by exacerbating angiogenesis through direct targeting of the tumor suppressor phosphatase and tensin homolog (PTEN) [111]. In addition, miR-34a-5p in CAF-derived exosomes in OSCC can stimulate the proliferation and metastasis of oral cancer cells by activating the AKT/glycogen synthase kinase-3 beta/β-catenin/Snail signaling cascade [136]. A recent investigation has shown that extreme metastatic oral squamous cell carcinoma cells secrete exosomes containing miR-1246 and -342-3p, which enhance the oncogenic growth, metastasis, and invasion of recipient cells [110]. The transformation of poor metastatic cells into aggressive metastatic cells is facilitated by the downregulation of the Multiple Acyl-CoA Dehydrogenase Deficiency (MADD)/DENN domain containing protein 2D (DENN2D) via the influence of exosomal miR-1246. Additionally, exosomes containing miR-21 exhibit increased expression of mesenchymal markers, such as vimentin and snail, and decreased expression of E-cadherin. These findings collectively suggest that OSCC malignant cell clusters undergo EMT and migrate to distant organs [202–204].

Lymphangiogenesis, the process of forming new lymphatic vessels, has been recognized as a novel prognostic indicator for predicting the risk of lymph node metastasis (LNM) [205]. During the progression of lymphatic metastasis, lymphatic vessels at the tumor periphery function as conduits for the dissemination of tumor cells to regional lymph nodes (LNs) [206]. Several cytokines, including vascular endothelial growth factor C (VEGF-C) and VEGF-D, engage with vascular endothelial growth factor receptor-3 (VEGFR-3) to stimulate the proliferation, tube formation, and migration of lymphatic endothelial cells (LECs) within the tumor microenvironment [207]. In various experimental tumor models, inhibition of the VEGF-C/VEGFR-3 signaling pathway was found to significantly reduce LNM by approximately 60–70% [208, 209], the effectiveness and side effects of these drugs still need to be carefully evaluatedNotably, some patients with esophageal squamous cell carcinoma (ESCC) with LNM display low levels of VEGF-C. Consequently, the identification of novel lymphangiogenesis regulators is crucial. Recent studies have revealed that miR-10527-5p, which is derived from ESCC-derived exosomes, exhibits potent inhibitory effects on the migration, invasion, and EMT of ESCC cells as well as

the migration and tube formation of human lymphatic endothelial cells. This inhibitory activity prevents lymphatic metastasis and lymphangiogenesis of ESCC through the Wnt/β-catenin signaling pathway by directly targeting Rab10 [155]. In contrast, ESCC-derived exosomal miR-320b has been found to induce the metastasis of human lymphatic endothelial cells (HLECs) and lymphatic metastasis by promoting EMT through direct targeting of PDCD4 [114]. More studies about the role of exosomal miRNAs derived from other types of tumor cells are shown in Table 2.

Conclusion

The propensity of cancer cells to colonize specific organs and tissues, a phenomenon known as organ-specific metastasis, is a complex process governed by a delicate interplay of genetic and environmental factors. Tumor-derived exosomes exert a pivotal role in the orchestration of organ-specific metastasis by facilitating the transfer of a distinct repertoire of pro-metastatic cargo between cancer cells and the target organ microenvironment. Exosomes derived from primary tumors exhibit a selective enrichment for specific biomolecules, including transcriptional regulators, growth factors, and adhesion molecules, which are instrumental in inducing a pre-metastatic niche in recipient cells, thereby enabling them to undergo EMT and adapt to the foreign microenvironment. The selective loading of exosomes with pro-metastatic molecules enables cancer cells to "pre-condition" the target organ microenvironment, thereby increasing their likelihood of successful colonization and growth.

Exosomal miRNAs have been demonstrated to exert a profound impact on the selective metastatic process, facilitating the establishment of metastatic niches by modulating gene expression through selective targeting of recipient cells. Exosomal miRNAs orchestrate the preparation of the pre-metastatic niche, a complex microenvironment that facilitates the homing and colonization of cancer cells at distant sites. By regulating the expression of genes involved in inflammation, angiogenesis, and immunosuppression, exosomal miRNAs create a permissive microenvironment that fosters a pro-tumorigenic landscape conducive to metastasis. Conversely, these miRNAs also repress the expression of genes involved in immune surveillance and tissue repair, thereby generating an environment that enables cancer cells to establish a foothold and thrive. This dual function of exosomal miRNAs underscores their pivotal role in shaping the microenvironmental conditions that enable cancer cell metastasis, making them attractive targets for therapeutic exploitation [29, 210]. Furthermore, these exosomal miRNAs have been identified as potential biomarkers for cancer diagnosis and monitoring, owing to their unique profiles and dynamic expression patterns. In fact, the TDEs emerge as a prime candidate for the development of prognostic biomarkers for PMNs, boasting a trifecta of attributes that render them particularly well-suited for this purpose: their remarkable stability, widespread presence in bodily fluids, non-invasive accessibility, and tumor-specific expression patterns [211]. However, a striking disparity is observed in the research landscape regarding the role of exosomal microRNAs in selective metastasis across distinct cancer types. For instance, while their involvement in lung and breast cancer metastasis has been extensively explored, analogous investigations remain scarce for other tumor types, such as pancreatic or ovarian cancer. This observation underscores the need for comprehensive and organ-specific studies to elucidate the underlying mechanisms driving exosomal microRNA-mediated selective metastasis in each cancer type. By deciphering these mechanisms, researchers may uncover novel therapeutic targets and develop more effective strategies for preventing and treating cancer metastasis, ultimately improving patient outcomes.

Over the past three decades, groundbreaking discoveries in the elucidation of cancer metastasis have unveiled a plethora of novel targets for preventing this insidious process. Notably, significant strides have been made in modulating the biochemical pathways and signaling cascades governing cell adhesion, dissociation, migration, invasion, and the complex interactions between cancer cells and the tumor microenvironment (TME). These advances have significantly expanded our understanding of the intricate mechanisms underlying cancer dissemination, thereby providing a rich source of opportunities for therapeutic interventions aimed at thwarting the metastatic process [9]. The development of exosomal miRNA-based therapeutics holds great promise, with potential treatments focused on inhibiting the transfer of these molecules to prevent reprogramming of recipient cells. Elucidating the specific receptors and ligands involved in targeting will enable the design of targeted therapies to block this interaction. Moreover, exosomal miRNAs may serve as non-invasive biomarkers for early detection of metastasis, revolutionizing diagnostic capabilities. The exploration of combination therapies targeting multiple components will also be crucial in combating this complex disease. Ultimately, a deeper understanding of exosome biology will inform the development of novel therapeutic approaches, paving the way for improved patient outcomes and a more effective treatment landscape for cancer.

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