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REVIEW

The Role of Exosomal MicroRNAs in Cancer Metastasis: An In-depth Guide

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SUMMARY

Exosomes and their contents play a vital role in forming a unique communication system that carries and transmits signal molecules, which alter the physiological state of cells and are linked to the onset and progression of numerous diseases including cancers. Focusing on exosomal cargo, microRNAs (miRNAs), which are small non-coding, single-stranded RNAs that regulate gene expression of target genes, are suggested to be transferred via exosomes in a selective manner that facilitates cancer progression and dissemination. In this context and through ongoing cancer research, researchers have currently been focusing on exosomal microRNA as a specific communication message delivered from cancer cells to the other cells that plays a crucial role in the immune response, tumor migration, tumor cell invasion, and development of metastasis In this review, we aim to evaluate the expected role of exosome-derived microRNAs in the development of cancer metastasis and their possible role of molecular markers in metastasis sites by the current literature on cancer research.

Keywords: Cancer; exosomal microRNAs; metastasis.

INTRODUCTION

Exosomes are subcellular vesicles with a diameter of 30–100 nm, surrounded by a lipid bilayer membrane. They have been identified in almost all bodily fluid, including blood, sweat, tear, urine, saliva, breast milk, ascites, and cerebrospinal fluid. Exosomes show heterogeneous compositionconsisting of a complex array of proteins, lipids, and nucleic acids (DNA, mRNA, and miRNA) found both inside and on their surface, reflecting the characteristics of the cell type that produced them. Exosomes are known to play a vital role in establishing a unique communication system throughcarrying and transmitting signaling molecules that alter the physiological state of the cells. They are also linked to the onset and progression of various diseases,including cancer. In this context, researchers, in an ongoing cancer research, have revealed their functions in immune response, tumor migration, and tumor cell invasion.[1]

Focusing on the exosomal cargo, scientists have currently been concentrating on exosomal miRNA as a specific communication message delivered from cancer cells to other cells after many years of research on the roles of miRNAs in cancer biology and therapy. This exosomal miRNA has an important role in the proliferation and migration of the tumor cell. MicroRNAs (miRNAs) are small [19–25 nucleotides), noncoding, single-stranded RNAs that regulate gene expression by binding imperfectly to the 3′ untranslated region (UTR) of target genes.[2,3] Over than 60% of all

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human genes are suggested to be directly regulated by miRNAs, as a single miRNA can target several hundred genes, and a single target gene generally contains multiple miRNA binding sites.[4]

In addition to their advantages in terms of quantity, quality, and stability, several studies have reported significant variations in the levels of exosomal miRNA and free circulating miRNA in healthy individuals and those with pathological conditions including cancer. However, no significant differences were detected in their levels among healthy individuals.[5–7] These findings suggest that the selective transfer of miRNAs through exosomes facilitates cancer progression and dissemination. The above discussed observations have recently led scientists and researchers to focus on the significance of investigating the role of exosomal miRNAs in cancer biogenesis and progression. In the present review, we will examine the recent studies on exosomal miRNAs, which are suggested to play an important role in cancer metastasis in various cancer types, and explore the potential mechanisms underlying their involvement in the progression of metastasis.

THE POTENTIAL MECHANISMS OF EXOSOMAL miRNAs IN METASTASIS

The studies in the last decades have supported the early ideas regarding metastasis evolution, known as the "seed and soil" hypothesis, which held that cancer cells seed metastasis through a series of orderly steps to a compatible tissue microenvironment.[8] These steps can be summarized as the loss of cellular adhesion, increased motility and invasiveness, entry and survival in the circulation, exit into new tissue, and colonization of a distant site.[9] Because the molecular process underlying tumor metastasis is still complex and not fully understood, numerous research published since 2007 have demonstrated the function of miRNA in activating or preventing metastasis at various stages of the metastatic pathway.[10–12] In the same context, various studies have highlighted the role of cancer secreted miRNAs by exosomes in controlling many cellular components of the tumor microenvironment, facilitating metastasis.[12] Although all mechanisms are interrelated, they can be categorized as follows for better clarification:

Promoting Angiogenesis and Vascular Permeability

Angiogenesis is the process of generating new blood capillaries from the existing vasculature. The role of this process is crucial in several physiological activities including embryonic development, female reproductive processes, and tissue repair. It also plays a significant function in pathological states such as inflammatory disorders and cancer.[13] The basic steps of sprouting angiogenesis include enzymatic degradation of capillary basement membrane, proliferation of endothelial cells (ECs), directed migration of ECs, tubulogenesis (ECs tube formation), vessel fusion, vessel pruning, and pericyte stabilization.[14]

To summarize the molecular mechanism of angiogenesis, hypoxia-inducible factor-α (HIFα) is reported to have a crucial role as a transcription factor in the signaling processes associated with angiogenesis. HIFα initiates the activation and subsequent release of vascular endothelial growth factor (VEGF), which then binds to its receptors VEGFR1 and VEGFR2 on endothelial cells (ECs), triggering downstream signaling pathways (ERK, p38 MAPK, and p125FAK, etc.) that lead to the activation of endothelial cells.

The activation of endothelial cells (ECs) is mediated by numerous secreted factors, including matrix metalloproteinases (MMPs), which is important in facilitating EC migration and promoting vascularization. In addition to HIFα, other transcription factors such as Activator Protein-1 (Ap1) and Specificity Protein-1 (Sp1) have been suggested to exert regulatory effects on VEGF expression by binding to its promoter region. Conversely, NFκB is known to facilitate the upregulation of VEGF, thus enhancing the process of angiogenesis. Furthermore, the potential contribution of the SMAD and NOTCH signaling pathways has been proposed in the stimulation of the migration of endothelial cells and the promotion of angiogenesis.

Poliseno et al.[15] were the first to propose the possible participation of microRNAs (miRNAs) in the process of angiogenesis in 2006. Their observation of the regulatory functions of certain miRNAs in modulating the expression of receptors for angiogenic factors supported their hypothesis. Subsequently, various studies investigated the miRNAs as a component of exosomes, which are considered an important intercellular communication mode in cancer progression to explore their involvement in promoting angiogenesis and vascular permeability and to explore their target genes.

Researchers suggested that specific miRNAs in nasopharyngeal carcinoma may contribute to the suppression of testis-specific gene antigen (TSGA10) expression following their transfer from cancer cells to endothelial cells (ECs) via exosomes. TSGA10 is known to closely interact with hypoxia-inducible factor-1

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(HIF-1α) and exert potent inhibitory effects on tumor angiogenesis and metastasis.[16–18] The inhibition of SMAD4 and STAT6 expression is another possible target of exosomal miRNAs in which STAT6 depletion reduces the inhibitory effects of interleukin-13 (IL-13) on human coronary artery endothelial cell migration and tube formation.[19] In colorectal cancer, exosomal miR-25-3p was shown to selectively target the transcription factors Kruppel-like factor KLF2 and KLF4, leading to the down regulation of ZO-1, Occludin, and Claudin5, and the up regulation of VEGFR2.[20] Similarly, miR-182-5p employs a similar mechanism to promote vascular permeability and angiogenesis in glioblastoma.[21] Targeting of prolyl-hydroxylase (PHD1 and PHD2) and the consequent accumulation of (HIF-1α) in endothelial cells by exosomal miR-23a enhances angiogenesis process in lung cancer.[22]

Mediating the Induction of EMT

Exosomal miRNAs are well-recognized as the components of complex regulatory networks that facilitate the transition in gene expression from an epithelial to a mesenchymal phenotype, a process described as the epithelial-to-mesenchymal transition (EMT). This transition is pivotal in driving the malignant transformation of epithelial cancer cells and promoting metastasis.[23,24] In this process, epithelial cancer cells lose the expression of epithelial markers, such as E-cadherin, occludin, claudins, ZO-1, and connexins, while they acquire mesenchymal markers, including N-cadherin, vimentin, and fibronectin. These morphological and molecular alterations enhance the metastatic potential of cancer cells.[25] Numerous molecular pathways have been identified to have involved in exosomal miRNAs in the regulation of epithelial-to-mesenchymal transition (EMT). The activation of the Wnt/β-catenin signaling pathway, which is a trigger of the EMT process, is one of the most frequently targeted pathways by exosomal miRNAs.[26] Exosomal miRNAs may also regulate additional signaling pathways, including PI3K/AKT and ERK pathways.[27,28]

As previously discussed, cancer-secreted miRNAs may promote the formation of a pre-metastatic niche by downregulating the Krüppel-like factor-2 (KLF2) and Krüppel-like factor-4 (KLF4) genes, members of the zinc finger-containing transcription factor family. These factors regulate the expression of tight junction (TJ) proteins, including ZO-1, occludin, and Claudin5, as well as the expression of VEGFR2 in endothelial cells.[20] In the similar context, the suppressing Krev interaction trapped protein-1 (KRIT1), key regulator of endothelial cell–cell junctions,[29] and subsequently activation of the β-Catenin signaling pathway represent another proposed mechanism through which exosomal miRNAs contribute to EMT process.[30] Endothelial junction integrity could also be compromised by the direct repression of p120 expression through specific exosomal miRNAs (exomirs).[31] Additionally, the down-regulation of the tumor suppressor gene CUGBP Elav-Like Family Member 2 (CELF2), via WW domain-containing oxidoreductase (WWOX) provides a further molecular mechanism underlying the role of exosomal miRNAs released from cancer-associated fibroblasts (CAFs) in colorectal cancer.[32]

Promoting Migration, Invasion, and Metastasis

The two distinct patterns of invasive growth are currently recognized as the collective cell migration and single-cell migration (also known as individual migration). In collective cell migration, the entire clusters of cancer cells infiltrate the surrounding tissues as cohesive units, either originating from or detaching from the primary tumor mass. These cells remain interconnected through adhesion molecules such as cadherins and intercellular gap junctions. In this process, tumor cells utilize integrins to form focal connections with the actin cytoskeleton, facilitating the proteolytic degradation of the extracellular matrix (ECM). This degradation creates a permissive environment for tumor invasion, which is essential for effective tumor cell migration. This mechanism is crucial for ensuring the effective migration of tumor tissue. In contrast, single-cell invasion involves independent migration of individual tumor cells into the surrounding tissues, which can occur through mesenchymal, and amoeboid movement modes. The transitions between these phenotypes are often driven by the changes in the activity of specific cellular molecules, allowing tumor cells to adapt to the unique characteristics of their microenvironment.[33]

A critical component of invasion involves the enzymatic breakdown of the extracellular matrix (ECM) and its components, facilitated by enzymes such as matrix metalloproteinases (MMPs). MMPs also play a crucial part in the process of invasion in addition to their significant contribution to cell proliferation, survival and angiogenesis. Furthermore, the initiation of distinct signaling pathways, such as the epidermal growth factor receptor (EGFR) signaling pathway and phosphatidylinositol 3-kinase (PI3K) pathway, stimulates the promotion of cancer cell proliferation and invasion.[34,35]

Numerous studies suggested that the exosomal microRNAs (miRNAs) regulate key cellular processes involved in cancer cell dissemination and metastasis, including migration and invasion. To exemplify, the exosomal miRNAs have been shown to target vascular endothelial growth factor A (VEGFA) in ovarian cancer cells, thereby influencing these processes.[36] Furthermore, cancer-derived exosomal microRNAs are implicated in extracellular matrix (ECM) remodeling and metastasis by activating cancer-associated fibroblasts (CAFs), which play a critical role in tumor progression.[37,38] Conversely, CAFs can enhance metastasis by secreting miRNAs via their own exosomes, which are subsequently delivered to cancer cells. This exchange promotes stemness, epithelial-to-mesenchymal transition (EMT), migration, and invasion in cancer cells.[39–42]

Tumor Microenvironment Remodeling

The tumor microenvironment (TME) is a complex and dynamic structure comprising various cell types embedded within a modified extracellular matrix (ECM).[43] Tumor-derived exosomes and their cargo play a pivotal role in mediating intercellular communication between tumor and non-tumor cells, thereby contributing to the remodeling of the TME and including its heterogeneity. The processes facilitate tumor development, invasion, and metastasis.[44] The effects of exosomal miRNAs on the tumor microenvironment (TME) can be categorized into two primary functional classifications within the context of tumor growth and progression.

The Process of Reshaping the Extracellular Matrix (ECM)

Tumor-derived exosomal miRNAs have the capacity to initiate a cascade of signaling pathways that drive the transformation of normal fibroblasts (NFs), which are responsible for producing the extracellular matrix (ECM) into cancer-associated fibroblasts (CAFs). This transformation alters the physiological properties of the ECM, creating a microenvironment conducive to cancer cell proliferation.[45] The activation of fibroblasts by cancer-driven exosomal miRNAs is associated with the upregulation of key markers including α-smooth muscle actin (α-SMA), fibroblast growth factor 2 (FGF2), and fibroblast activating protein (FAP).[46,47]

Over the last decade, the increasing evidence has highlighted the involvement of exosomal miRNAs in the regulation of ECM remodeling. Wang et al.[48] demonstrated that exosomal miR-27a from gastric cancer (GC) cells is transferred to fibroblasts, leading to decreased CSRP2 expression, increased α-SMA expression, and fibroblast differentiation into cancer-associated fibroblasts (CAFs). Similarly, a 2019 study revealed that exosomal miR-124 plays a role in ECM remodeling by targeting sphingosine kinase 1 (SPHK1), thereby upregulating α-SMA and FAP expression and promoting the differentiation of NFs into CAFs in ovarian cancer.[49] Furthermore, the transfer of exosomal miR-10b from colorectal cancer cells to fibroblasts results in the downregulation of PIK3CA expression, reduced activity of the PI3K/Akt/mTOR signaling pathway, increased TGFβ and α-SMA expression, and the acquisition of CAF-like properties by fibroblasts.[50]

The Process of Mediating Inflammatory Cell Invasion, and Immunological Evasion

Tumor cells have the ability to disrupt the maturation and differentiation of immune cells by releasing exosomal microRNAs, which activate multiple signal transduction pathways. This ultimately leads to the establishment of an immunosuppressive microenvironment that supports tumor proliferation. Concurrently, the production of inflammatory mediators by tumor cells such as prostaglandins and arachidonic acid, fosters the development of an inflammatory microenvironment. In this context, exosomal miRNAs contribute to the stimulation of extracellular receptor signaling, disruption of cell adhesion, and maintenance of a chronic low-grade inflammatory state, collectively facilitating the evasion of tumor cells from immune surveillance.[51,52]

Tumor-derived exosomal miRNAs also have the capacity to influence the maturation and functioning of dendritic cells (DCs), which serve as antigen-presenting cells crucial for initiating T cell activation and sustaining immunological responses. To examplify, the tumor-derived exosomes containing up-regulated exosomal miR-let-7i can be internalized by myeloid dendritic cells (mDCs), modulating intracellular levels of cytokines and signaling molecules such as IL-6, IL-17, IL-1b, TGF-β, SOCS1, KLRK1, IFNγ, and TLR4, thereby suppressing immune response.[53] Similarly, tumor-associated macrophages (TAMs) represent another subset of immune cells affected by exosomal miRNAs, as numerous studies have demonstrated their involvement in modulating TAM phenotypes.[54] For instance, in epithelial ovarian cancer (EOC), the transfer of exosomal miR-222-3p to

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macrophages leads to the downregulation of SOCS3, which in turn promotes STAT3 phosphorylation and subsequent polarization of macrophages toward the immune-suppressive M2 phenotype.[55]

This review aims to analyze the recent studies published in PubMed that focuses on the role of exosomal miRNAs in malignancies, with an emphasis on identifying the most significant exosomal miRNAs implicated in metastasis across various cancer types.

EXOSOMAL miRNAs ASSOCIATED WITH METASTASIS

Exosomal miRNAs Associated with Metastasis in Breast Cancer

Santos et al.[56] demonstrated the role of exosomal miR-155 in the activation of epithelial-mesenchymal transition (EMT) markers and the downregulation of E-cadherin in breast cancer cells exposed to exosomes derived from cells with elevated miR-155 expression. The process was previously described in a study which identified the role of miR-155 in depleting C/EBPβ, thereby enhancing the TGF-β response and promoting EMT.[57] The promotion of EMT by miR-155 has been observed in several other cancer types in addition to breast cancer cells which will be further discussed.

Researchers in another study reported that exosomal miR-21, miR-378e, and miR-143 derived from cancer-associated fibroblasts (CAFs) in breast cancer, contribute to the enhancement of cancer stemness and EMT.[58] In addition, breast cancer-derived exosomal miR-146a has been shown to accelerate the differentiation of normal fibroblasts (NF) into cancer-associated fibroblasts (CAFs), thereby promoting cell invasion and migration. miR-146a targets the TXNIP gene -a well-known metastasis suppressor, by modulating the Wnt signaling pathway.[59] Similarly, exosomal miR-9 facilitates this transformation by influencing the expression of MMP1, EFEMP1, and COL1A1.[60]

Exosomal miR-105, on the other hand, activates MYC signal transduction, enabling CAFs to adapt to various metabolic conditions and thereby enhancing tumor progression.[61] Although the exact mechanism remains unclear, significantly elevated levels of exosomal miR-7641 in the plasma of breast cancer patients with distant metastasis suggest a potential role in promoting tumor cell progression and metastasis.[62] Additionally, researchers in a recent study revealed that exosomal miR-19a in estrogen receptor-positive breast cancer promotes osteolytic bone metastasis by suppressing PTEN expression, which subsequently activates the NF-κB and AKT signaling pathways.[63]

Exosomal miRNAs Associated with Metastasis in Liver Cancer

Elevated serum exosomal miR-1247-3p levels correlate with lung metastasis in hepatocellular carcinoma (HCC) patients. This correlation is mediated by the direct targeting of B4GALT3, which subsequently activates the β1-integrin-NF-κB signaling pathway in fibroblasts.[38] In the same context, hepatoma cell-secreted miR-103 might be transferred into endothelial cells via exosomes. This transfer leads to the attenuation of endothelial junction integrity by inhibiting the expression of VE-Cadherin (VE-Cad), p120-Catenin (p120), and zonula occludens, ultimately resulting in increased vascular permeability and facilitating metastasis.[31] Furthermore, the transfer of exosomal miR-210 from HCC cells to endothelial cells can promote angiogenesis by targeting SMAD4 and STAT6 in endothelial cells.[19] The transmission of exosomal miR-21 to cancer-associated fibroblasts (CAFs) stimulates PDK1/Akt signaling through direct targeting of PTEN. The activation leads to the increased expression of factors such as VEGF, MMP2, MMP9, bFGF, and TGF-β, thus facilitating the progression of angiogenesis.[64]

Exosomal miRNAs Associated with Metastasis in Lung Cancer

The release of exosomal miR-23a by lung cancer cells under hypoxic conditions has been shown to selectively target prolyl-hydroxylase and the tight junction protein ZO-1, thereby enhancing angiogenesis and increasing vascular permeability.[22] of Mao et al.[65] provided evidence supporting the angiogenic properties of miR-494 in non-small cell lung cancer, demonstrating its effect through the activation of the Akt/eNOS pathway following the targeting of the PTEN gene. In a different mechanism, exosomal miR-21 and miR-29 from lung cancer cells contribute to the formation of an inflammatory microenvironment. These exosomes act as ligands for Toll-like receptors (TLRs) on immune cells, thereby activating a TLR-mediated prometastatic inflammatory response, which can promote tumor growth and metastasis.[66] Additionally, exosomal miR-1260b is suggested to facilitate cell invasion in lung cancer cells by regulating the Wnt/-catenin signaling pathway through the suppression of sFRP1 and Smad4 in lung adenocarcinoma.[67]

Exosomal miRNAs Associated with Metastasis in Colorectal Cancer

Researchers in a recent study demonstrated that colorectal cancer (CRC) secretes exosomal miR-25-3p, which plays a role in enhancing vascular permeability and angiogenesis. This occurs through the silencing of KLF2 and KLF4, leading to the disruption of tight junctions in endothelial cells. Consequently, this mechanism contributes to the formation of pre-metastatic niches in distant organs such as lung and liver.[20] Elevated levels of exosomal miR-21 derived from the plasma of patients with colorectal cancer (CRC) have been found to correlate with liver metastasis and TNM stages.[68,69] Moreover, a recent study elucidated the mechanism by which miR-21 suppresses Krev interaction trapped protein 1 (KRIT1) and activates the β-catenin signaling pathway, thereby inducing angiogenesis and vascular permeability.[30] Exosomal miR-92a-3p derived from CAFs may promote stemness, invasion, metastasis, and EMT in colorectal cancer by targeting tumor suppressor genes FBXW7 and MOAP1.[41] These findings align with a subsequent study which demonstrated the role of hepatoma-derived exosomal miR92a-3p in promoting EMT and metastasis by inhibiting PTEN and activating the Akt/Snail signaling pathway.[70] Another CAF-derived exosomal miRNA, miR-17-5p, increases CRC metastatic potential by directly targeting RUNX family transcription factor 3 (RUNX3) in CRC cells. RUNX3 interacts with the proto-oncogene MYC, thereby stimulating the TGF-β signaling pathway.[71] The induction of fibroblasts to acquire the characteristics of cancer-associated fibroblasts (CAFs) in colorectal cancer may be facilitated by exosomal miR-10b. This outcome is achieved by inhibiting the PI3K/Akt/mTOR pathway and promoting the production of transforming growth factor-beta (TGF-β) and alpha-smooth muscle actin (α-SMA).[50]

Exosomal miRNAs Associated with Metastasis in Other Different Cancers

Li et al.[72] demonstrated that the hypoxic microenvironment can stimulate oral squamous cell carcinoma cells (OSCC) to produce miR-21-richexosomes, which are then delivered to normoxic cells, inducing a pro-metastatic phenotype. The involvement of miR-21 in EMT and metastasis has been previously described, where it targets the AKT/ERK1/2 pathway and PTEN.[28]

Angiogenesis is facilitated by the repression of a recently discovered target gene, testis-specific gene antigen 10 (TSGA10), which functions as a tumor suppressor in several types of malignancies. In nasopharyngeal cancer, exosomal miR-23a promotes metastasis by targeting this gene.[16,18] The study of Yang et al.[73] provided evidence for the role of exosomal miR-423-5p in inhibiting the production of suppressor of fused protein (SUFU), which consequently affects the proliferation and migration of gastric cancer. Meanwhile, miR-27a derived from gastric cancer (GC) is transported to fibroblasts and promotes their differentiation into CAFs by downregulating the expression of CSRP2, a protein involved in regulatory processes essential for cellular differentiation.[48] Several studies have suggested that microvesicles released from human renal cancer stem cells stimulate angiogenesis and the formation of a lung pre-metastatic niche.[74] Exosomal miR-155-5p derived from hypoxic tumor-associated macrophages (TAMs) plays a role in enhancing the stability of the transcription factor IGF1R mRNA. This, in turn, facilitates the proliferation and metastasis of renal cell carcinoma [RCC] cells by upregulating the phosphorylation of PI3K, p85, and AKT.[27] Conversely, the loss of exosomal miR-148b released from cancer-associated fibroblasts (CAFs) in endometrial cancer has the potential to increase the expression of DNMT1. This process leads to changes in several molecules associated with epithelial-mesenchymal transition (EMT), including E-cadherin, N-cadherin, vimentin, and fibronectin, ultimately promoting metastasis of cancer cells. Enhancing the transfer of stromal cell-derived miR-148b may thus represent a potential strategy for preventing the progression of endometrial cancer[75] (Table 1).

CONCLUSION

Following the discovery of exosomes and over the past three decades of research, our data on exosomes has expanded, and the functions of exosomes in different physiologic and pathologic conditions, including cancer, have been explored. In this context, recent advancements in cancer research have highlighted the importance of exosomes and their cargo, particularly miRNAs, in cancer progression and metastasis. Several studies indicate the critical role of exosomes as intercellular messengers, contributing to the remodeling of both the local and distant microenvironments. Furthermore, exosomes can effectively trigger both pro-tumor and anti-tumor immunological responses;

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Table 1 Overview of exosomal microRNAs and their potential mechanisms involved in cancer metastasis over the last decades

Exosomal microRNAs	Cancer	Source	Biological activities	Potential mechanisms	Year	Refs
miR-155 & miR-155-5p	Breast cancer\ BC	Cancer cells	Epithelial-mesenchymal transition (EMT)	Induction of TGF-β signaling and reduction of C/EBP-β	2015	[56,57]
	Non-small cell lung cancer\ NSCLC	Tumor associated macrophages (TAMs)	Migration, Invasion & Epithelial-Mesenchymal Transition (EMT)	Negatively Regulating RASSF4 Expression (a tumor suppressor)	2021	[76]
	Gastric cancer	Cancer cells	Angiogenesis	Up-regulating VEGF Expression and Inhibiting c-MYB	2020	[77]
				Inhibition of (FOXO3a) Expression (a tumor suppressor gene)	2019	[78]
	Renal cell carcinoma\ RCC	Hypoxic TAM	Proliferation & metastasis	Increase of IGF1R stability & activation of PI3K/AKT pathway	2021	[27]
	Multiple myeloma\ MM	Cancer cells	Angiogenesis	Up-Regulation of VEGF-α, FGF2, and MMP9 & Down-Regulation of SOCS1-JAK2/STAT3 Signaling Pathway	2018	[79]
	Colorectal cancer\ CRC	CRC cells	Activation of cancer-associated fibroblasts CAFs, EMT & Invasion	Down-Regulation of SOCS1 & Activation of JAK2-STAT3/NF-κβ Signaling pathway	2022	[80]
miR-21	Breast cancer	CAFs	EMT	-	2017	[58]
		Tumor cells	Osteoclastogenesis & bone metastasis	Regulation of PDCD4 protein levels	2021	[81]
					2018	[64]
	Hepatocellular carcinoma\ HCC	HCC	Angiogenesis	Activation of PDK1/AKT pathway Up-regulating VEGF, MMP2, MMP9, BFGF, and TGF-β expression	2019	[82]
	Lung cancer	Lung cancer cell line	Activation of toll-like receptor TLR-mediated inflammatory response, tumor growth&metastasis	Function as TLR ligands in immune cells	2012	[66]
		Metastatic lung cancer cells	Macrophage polarization, EMT & brain metastasis	ERK/STAT3 signaling acceleration	2023	[83]
	Colorectal cancer\ CRC	Plasma	Angiogenesis & vascular permeability	KRIT1 suppression	2021	[30]
				β-catenin signaling pathway activation	2017	[69]
		CRC cells & plasma	Inducing an Inflammatory Pre-metastatic niche & liver metastasis	miR-21-TLR7-Il-6 Axis targeting	2018	[68]
	Oral squamous cell carcinoma \ OSCC	Hypoxic OSCC	Migration, invasion & metastasis	Enhancing snail and vimentin expression; decreasing e-cadherin levels in OSCC cells	2016	[72]
			EMT	Targeting of PTEN via inactivation of AKT and ERK1/2 pathways	2012	[28]
	Head and neck squamous cell carcinoma \ HNSCC	Hypoxic tumor cells	Metastasis	CAFs Activation by Targeting YOD1	2023	[84]
	Multiple myeloma\ MM	Melanoma cells	Invasion	Down-regulation of TIMP3 and up-regulation of mmp expression in fibroblast cells	2020	[85]

Table 1 Cont.

Exosomal microRNAs	Cancer	Source	Biological activities	Potential mechanisms	Year	Refs
	Esophageal squamous cell carcinoma / ESCC	ESCC cells	Proliferation and angiogenesis of human umbilical vein endothelial cells HUVECs	SPRY1 Down-regulation and VEGF Up-regulation	2020	[86]
	Gastric cancer	Peritoneal fluids	Peritoneal metastases (PM)	-	2020	[87]
	Renal cell carcinoma\ RCC	M2 macrophages	Promotion of metastatic features of renal cell carcinoma cells	PTEN/AKT signaling regulation by PTEN-3'UTR targeting	2022	[88]
miR-143	Gastric cancer	Plasma	Liver & ovarian metastasis	-	2020	[89]
miR-146a	Breast cancer	Breast cancer cells	CAFs activation, invasion & metastasis	WNT pathway activation by miR-146a/TXNIP axis targeting	2020	[59]
	Colorectal cancer\ CRC	Colorectal cancer\ CRC cells	CAFs activation, EMT & lung metastasis	JAK2-STAT3/NF-κβ signaling activation via SOCS1 & ZBTB2 targeting	2022	[80]
	Cervical cancer	Plasma	Early progression & metastasis	Up-regulating PCK1 expression & down-regulating Fcgr1a expression	2021	[90]
miR-9	Breast cancer	MDA-MB-231 & MCF-7 cells	Metastatic characteristics	PTEN and DUSP14 down-regulation	2019	[91]
	Nasopharyngeal carcinoma\ NPC	NPC cells	Inhibition of angiogenesis & migration	Regulation of PDK/AKT signaling pathway via MDK targeting	2018	[92]
	Renal cell carcinoma\ RCC	Renal cancer cells	Proliferation & invasion	Down-Regulation of SOCS4 expression, (JAK)/signaling inhibition & (STAT) pathway activation	2020	[93]
miR-105	Breast cancer	Breast cancer cells	Induction of migration & vascular permeability	Inhibition Of ZO-1 expression	2014	[12]
miR-7641	Breast cancer	Breast cancer cells	Tumor progression & metastasis	-	2021	[62]
miR-19a	Breast cancer	(ER+) breast cancer cells	Osteolytic bone metastasis in cooperation with IBSP	-	2021	[63]
miR-1247-3p	Hepatocellular carcinoma\ HCC	High-metastatic HCC cells	CAFs activation & lung metastasis ınduction	Activation of Beta1-integrin-NF-κβ signaling in fibroblasts	2018	[38]
miR-210	Lung cancer	Hypoxic bone marrow mesenchymal stem cell \BMSCs	Invasion & EMT	Activation of STAT3 signaling pathway	2019	[94]
		Lung CSC	Migration, invasion & metastasis	Interaction with fibroblast growth factor receptor-like 1 (FGFRL1) leading to FGFRL1 silencing	2020	[95]
	Colorectal cancer\ CRC	Human colon cancer cells	EMT promotion & adhesion of neighboring metastatic cells	E-cadherin positive regulation and vimentin negative regulation	2016	[96]
miR-103	Hepatocellular carcinoma\ HCC	Hepatoma cell	Increasing vascular permeability, tumor cell migration & tumor metastasis promotion	Inhibition of VE-cadherin, P120-catenin & zonula occludens 1 expression	2018	[31]

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Table 1 Cont.

Exosomal microRNAs	Cancer	Source	Biological activities	Potential mechanisms	Year	Refs
miR-23a	Nasopharyngeal carcinoma\ NPC	NPC cells	Angiogenesis	TSGA10 targeting	2018	[16]
	Hepatocellular carcinoma\ HCC	M2 macrophage	EMT, angiogenesis promotion & ıncrease of vascular permeability	(PTEN) & (TJP1) targeting	2023	[97]
miR-423-5p	Gastric cancer	Serum of gastric cancer patients	Proliferation & migration of gastric cancer cells	Inhibition of suppressor of fused protein (SUFU) expression	2018	[73]
miR-27a	Gastric cancer	Gastric cancer cells	CAFs activation, proliferation, motility & metastasis of cancer cells	Cysteine and glycine-rich protein 2 (CSRP2) down regulation	2018	[48]
	Hepatocellular Carcinoma\ HCC	Plasma	HCC lung metastasis	-	2021	[98]
miR-494	Breast cancer	RAS-activated breast cancer cells	Osteolytic bone metastasis induction	Enhancement of RANKL-induced osteoclast formation & inhibition of bone morphogenetic protein 2- by targeting semaphorin 3A	2023	[99]
	Multiple myeloma\ MM	Serum, human melanoma cell lines & *in vivo* mice model	Melanoma metastasis	-	2019	[100]
miR-29	Gastric cancer	Peritoneal fluids	Peritoneal metastases (PM)	-	2020	[87]
miR-1260b	Non-small cell lung cancer\ NSCLC	Non-small cell lung cancer cells & plasma	Angiogenesis	Homeodomain-interacting protein kinase 2 (Hipk2) suppression	2021	[101]
	Lung adenocarcinoma	Plasma & lung adenocarcinoma cells	Invasion	WNT/ β-catenin signaling pathway regulation by SFRP1 & SMAD4 inhibition	2020	[67]
miR-25-3p	Colorectal cancer\ CRC	Colorectal cancer cells	Vascular permeability & angiogenesis induction; liver & lung metastasis enhancing	KLF2 and KLF4 targeting; VEGFR2, ZO-1, occludin & claudin5 expression regulation	2018	[20]
			EMT & cancer metastasis promotion	PI3K/AKT signaling pathway	2020	[102]
miR-92a-3p	Colorectal cancer\ CRC	Colorectal cancer\ CRC cells	EMT & metastasis	WNT/ β-catenin pathway activation; FBXW7 & MOAP1 (tumor suppressor genes) inhibition	2019	[41]
	Hepatocellular carcinoma\ HCC	HCC cells	EMT progression & metastasis	PTEN inhibition & AKT/snail signaling pathway activation	2020	[70]
	Prostate adenocarcinoma	Serum	Osteoblastic metastases	-	2023	[103]
miR-17-5p	Non-small cell lung cancer	Lung cancer cells	Osteoclastogenesis	PI3K/Akt pathway inhibition via targeting PTEN	2021	[104]
	Colorectal cancer\ CRC	Plasma & colorectal cancer tissue	Liver metastasis	-	2021	[105]
		CAFs	COLORECTAL cancer metastasis	RUNX3 targeting & TGF-β signaling pathway activation	2020	[71]

Table 1 Cont.

Exosomal microRNAs	Cancer	Source	Biological activities	Potential mechanisms	Year	Refs
miR-10b	Hepatocellular carcinoma\ HCC	HCC cells	Cancer cell proliferation & metastasis	-	2019	[82]
	Lung cancer	A549 lung cancer cells	Invasion, EMT induction & M2 polarization of macrophages	-	2022	[106]
	Oral cancer \OC	Oral cancer cells	Invasion & migration of oral cancer cells	AKT signaling activation	2022	[107]
	Gastric cancer	Plasma	Metastasis	-	2020	[89]
miR-148b	Breast cancer	Breast cancer cells	Invasion, migration & M2 polarization of macrophages	Targeting TSC2 which controls cell growth and division	2023	[108]
	Endometrial cancer\ EC	CAFs and endometrial cancer cells	Suppression of endometrial cancer metastasis	Binding to its downstream target gene, DNMT1	2019	[75]

EMT: Epithelial-mesenchymal transition; TGF-β – Transforming growth factor-β; C/EBP β : CCAAT/enhancer-binding protein beta; TAMs: Tumor-associated macrophages; VEGF: Vascular endothelial growth factor; RASSF4: Ras association domain family member 4; c-MYB: Member of myeloblastosis family of transcription factors; FOXO: Forkhead box transcription factors; IGF1R: Insulin-like growth factor 1 receptor; PI3K: Phosphoinositide 3-kinase; FGF2: Fibroblast growth factor 2; CAFs: Cancer-associated fibroblasts; PDCD4: Programmed cell death protein 4; PDK1: Phosphoinositide dependent protein kinase-1; AKT: Protein kinase B; MMP: Matrix metalloproteinase; SOCS1: Suppressor of cytokine signaling; JAK2: Janus kinase 2; STAT3: Signal transducer and activator of transcription 3; NF-κβ: Nuclear factor kappa B; bFGF: Basic fibroblast growth factor; TLR: Toll-like receptor; ERK/STAT3: Extracellular signal-regulated kinase / signal transducer and activator of transcription 3; KRIT1: Krev interaction trapped protein 1; YOD1: Deubiquitinating enzyme; TIMP3: Tissue inhibitor of metalloproteinases 3; HUVECs: Human umbilical vein endothelial cell; SPRY1: Sprouty RTK signaling antagonist 1; PTEN-3'UTR: Phosphatase and tensin homolog 3′ untranslated region; TXNIP: Thioredoxin interacting protein; ZBTB2: Zinc finger and BTB domain containing 2; PCK1: Phosphoenolpyruvate carboxykinase 1; Fcgr1a: Fc gamma receptor 1A; DUSP14: Dual specificity phosphatase 14; MDK: Midkine (heparin-binding growth factor); MDA-MB-231: Model of late-stage triple-negative breast cancer; MCF-7: Michigan cancer foundation-7 (breast cancer cell line); ZO-1: Zonula occludens; ER+: Estrogen receptor positiv; IBSP: Integrin binding sialoprotein; BMSCs: Bone marrow-derived mesenchymal stem cells; TSGA10: Testis-specific gene 10 protein; TJP1: Tight junction protein 1 (another name for ZO-1); RANKL: Receptor activator of nuclear factor kappa-B ligand; SFRP1: Secreted frizzled-related protein 1; KLF2 and KLF4: Krüppel-like factor 2 and 4; FBXW7: F-box and WD repeat domain-containing 7; MOAP1: Modulator of apoptosis 1; RUNX3: Runt-related transcription factor 3; TSC2: TSC complex subunit 2; DNMT1: DNA methyltransferase 1.

however, in the advanced stage, exosomes derived from cancer cells exhibit higher levels of immune suppression compared with the levels in immune activation. These findings underscore the need for further research into the precise mechanisms governing exosomal cargo selection, their tissue-specific targeting, and the development of strategies to harness or modulate exosomal signaling for personalized cancer therapy and early detection of metastatic events.

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