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REVIEW

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Interactions between cancer and stroma mediated by extracellular vesicles

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Abstract

Extracellular vehicles (EVs) are small membrane-bound particles that are released by both cancer and stromal cells. These vesicles have emerged as key mediators of intercellular communication within the tumor microenvironment. In particular, EVs have been shown to play a critical role in facilitating the interactions between cancer cells and the surrounding stroma. Through the transfer of various bioactive molecules, including proteins, lipids, and nucleic acids, EVs are able to modulate the behavior of recipient cells and promote tumorigenesis. Additionally, EVs can also contribute to the development of drug resistance and immune evasion, further highlighting their importance in cancer progression. This review will summarize the current knowledge regarding EV-mediated interactions between cancer and stromal cells, and discuss their implications for cancer diagnosis and therapy.

Keywords Cancer, Tumor microenvironment, Extracellular vehicles

Introduction

Cancer is known as a major health concern on a global scale by causing 10 million deaths and 19.3 million incidences in 2020 [1]. The growth and development of cancer cells are intricately linked to the microenvironment surrounding them. The tumor microenvironment (TME) is a multifaceted and diverse network that encompasses all essential elements needed for the development and advancement of a tumor. The TME consists of various cellular components, including fibroblasts, endothelial cells (ECs), adipocytes, and immune cells. In addition to these cellular components, the extracellular matrix (ECM) is a critical non-cellular component of the TME. The ECM is composed of a network of polymeric proteins and other elements that play a critical role in shaping the TME and influencing tumor growth and development [2]. Interactions between stromal cells with tumor cells are important in tumor biology, directing cell signaling, proliferation, survival, and drug sensitivity [3].

Extracellular vesicles (EVs) have been identified as major mediators of communication between tumor and stroma. The three distinct groups of EVs that have been classified include exosomes, microvesicles, and apoptotic bodies. This classification is based on the size of the vesicles as well as the method through which they release materials into the intercellular space [4]. Exosomes are the smallest of the three types of EVs, typically ranging in size from 30 to 100 nm. They are known to be formed within endosomal organelles known as multi-vesicular bodies (MVBs) [5, 6]. One noteworthy aspect is that exosomes are not exclusive to the tumor microenvironment, but can be found in all bodily fluids, including urine, blood, and ascites. Exosomes are released both under normal physiological conditions

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and in pathological states [7]. Exosomes have emerged as a promising biomarker for detecting a wide range of pathological conditions due to their strong association with numerous diseases. Given the significant role of stromal-derived exosomes in tumorigenesis-related events, the objective of this review is to explore their impact on cancer cell biology.

Extracellular vesicle-mediated cross-connections between mesenchymal stem cells and *cancer* cells

Mesenchymal stem cells (MSCs) are a type of multipotent stromal cells that are found in a variety of different tissues and organs throughout the body [8, 9]. MSCs secrete exosomes that promote the growth and spread of breast cancer cells. The exosomes derived from MSCs contain microRNA-21 and microRNA-34a, which have been found to promote the proliferation and metastasis of breast cancer cells. Conversely, exosomal miRNA-16 downregulates the expression of vascular endothelial growth factor (VEGF) in ovarian cells, thereby inhibiting angiogenesis.

Exosomes have been shown to play a crucial role in the transmission of the Hedgehog signaling pathway and gradient formation [10].

Qi, Jin, and colleagues demonstrated that exosomes derived from human bone marrow mesenchymal stem cells (hMSCs) can stimulate the growth of osteosarcoma and gastric cancer cells through activation of the Hedgehog signaling pathway [11]. This research assessed several factors, including Smoothened, Patched-1, Gli1, and Sonic Hedgehog, which were upregulated and found to promote cancer cell growth [11]. Moreover, exosomes derived from human bone marrow mesenchymal stem cells have been found to activate the extracellular signal-regulated kinase1/2 (ERK1/2) pathway, leading to an upregulation of vascular endothelial growth factor (VEGF) and promoting tumor growth [12] (Fig. 1).

Alternatively, exosomes originating from human bone marrow mesenchymal stem cells inhibited the growth of

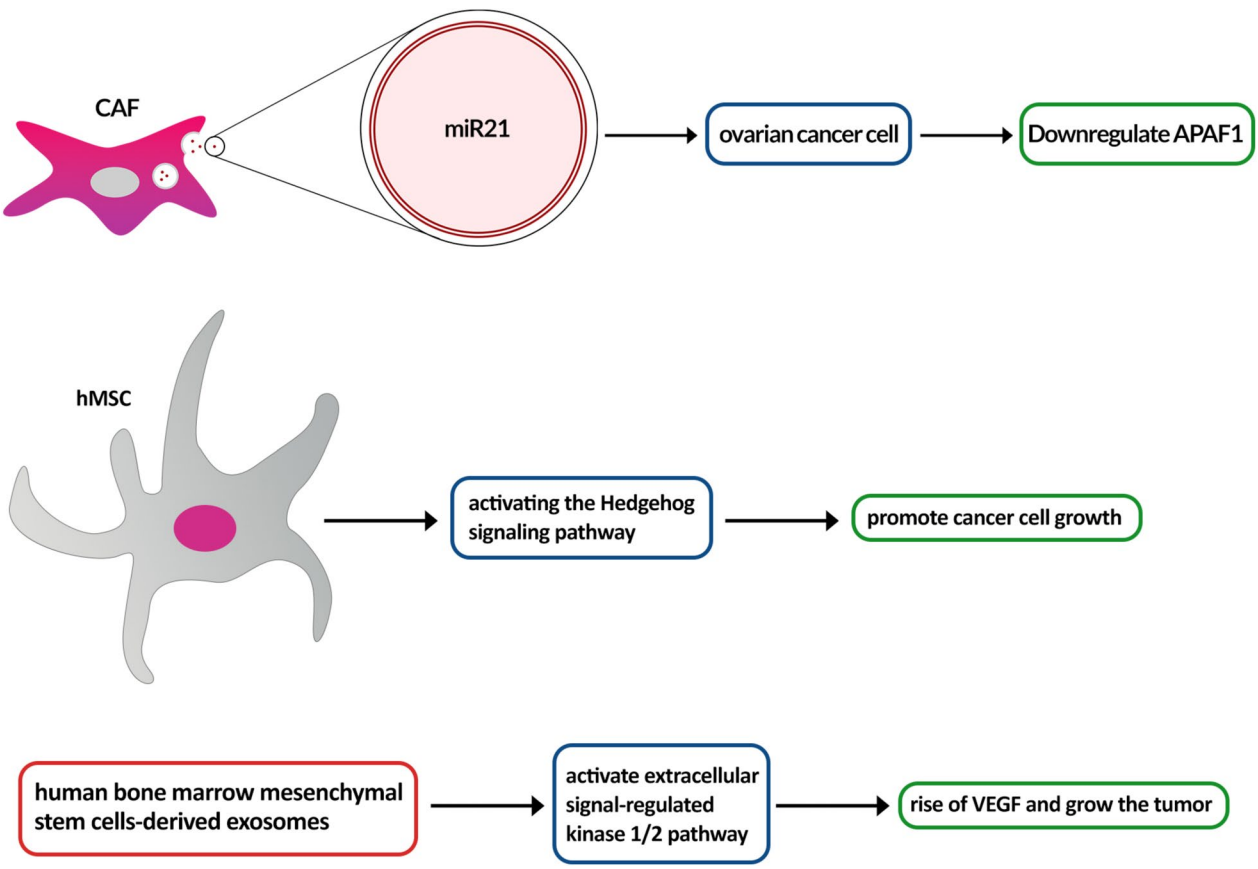

Fig. 1 CAF-derived exosomes contain MiR-21 can downregulate APAF-1 which results in downregulation of VEGF. Exosome derived from hMSC have a vital function in facilitating the transmission of the Hedgehog signaling pathway and the formation of signaling gradient. Exosome derived from human mesenchymal stem cell can activate ERK1/2 pathway. This activation results in an increase in vascular endothelial growth factor (VEGF) expression, ultimately promoting tumor growth

a bone marrow-metastatic human breast cancer cell line (BM2). This was linked to a decrease in the presence of stem cell-like surface markers, a lower invasiveness and a decreased responsiveness to docetaxel, a frequently utilized chemotherapy drug. Similar findings were obtained when the BM2 cells were cultured with exosomes obtained from BM-MSC cultures [13].

Different research has indicated that exosomes discharged by mesenchymal stem cells derived from bone marrow (BM-MSCs) carry miRNA that influences the behaviors of BM-MSCs. These exosomes derived from BM-MSCs of patients with multiple myeloma were found to promote tumor growth in vivo and accelerate the spread of cancerous cells to the bone marrow. Compared to exosomes derived from multiple myeloma BM-MSCs, exosomes derived from normal BM-MSCs had higher levels of miR-15a. Therefore, it appears that miR-15a may play a role in suppressing tumor growth in multiple myeloma [14].

Exosomes obtained from BM-MSCs have been demonstrated to impact cancer stem cells (CSCs) through the activity of microRNA-23b (miR-23b) as it has been verified that miR-23b is capable of causing effective effects on cancer cells invasions by triggering cell cycle arrest and suppressing the proliferation of the cancer cells through downregulation of MARCKS gene. The use of miR-23b led to the decreased expression of the CD44 as the major characteristic surface marker in breast cancer cells and initiation of the dormancy [15].

Mesenchymal stem cell-derived exosomes have the ability to modulate the function and phenotype of recipient cells through the regulation of intercellular communication. Recent research has demonstrated that mesenchymal stem cell-derived exosomes induce resistance to chemotherapy in gastric cancer cells by upregulating multidrug resistance protein (MDR), multidrug resistance-associated protein (MRP), and lung resistance protein (LRP), which are members of the multidrug resistance family. Exposure of gastric cancer cells to 5-fluorouracil both in vivo and ex vivo induced the release of exosomes, which, in turn, activated calcium/calmodulin-dependent protein kinases (CaM-Ks) and the Raf/MEK/ERK kinase cascade, ultimately leading to the overexpression of MDR, MRP, and LRP proteins [16].

Exosomes derived from human BM-MSCs are acknowledged for harboring multiple angiogenic factors that can influence angiogenesis in tumors. These exosomes can activate the ERK1/2 pathway, leading to an upregulation of VEGF expression in tumor cells. As a result, exosomes can have a positive impact on tumor growth by promoting angiogenesis [12]. Extracellular vesicles derived from placental MSCs and adipose MSCs can promote vascularization and angiogenesis, respectively. Adipose MSCs release exosomes that are enriched with proangiogenic factors and are capable of inducing angiogenesis, and it was shown that the secretion of exosomes from adipose MSCs is downregulated by platelet-derived growth factor (PDGF) [17]. On the other hand, according to another study, when breast cancer cells internalized exosomes derived from MSCs, it resulted in a downregulation in VEGF expression, which in turn inhibited angiogenesis. One of the constituents present in the exosomes was miR-16, which demonstrated the ability to downregulate VEGF expression in a breast cancer cell line (4T1) [18] (Fig. 2). Therefore, while MSC-derived exosomes have been shown to play a pivotal role in promoting tumor cell growth by upregulating VEGF expression in tumor cells, there are conflicting reports on the effects of MSC-derived exosomes on angiogenesis in breast cancer tissues. These divergent outcomes may be attributed to various factors, such as the heterogeneity of MSCs, differences in MSC doses, variations in tumor types, and contamination of MSCs [19].

MSCs isolated from cancerous tissue have been shown to secrete exosomes that contain a variety of microRNAs, including miR-214, miR-221, and miR-222. In particular, exosome-mediated transfer of miR-221 from MSCs to HGC27 tumor cells promotes tumor growth and increase tumor cell migration [17].

Similarly, another study demonstrated that exosomes originated from human mesenchymal stem cells (hMSCs) could enhance the migratory capabilities of the MCF-7 cell line. Treatment of MCF-7 cells with exosomes obtained from hMSCs resulted in the activation of various signaling pathways related to cancer. Notably, the WNT signaling pathway was observed to be upregulated in these cell lines [20]. MSC-derived microvesicles released into the tumor microenvironment enhance the proliferation and metabolic activity of breast cancer cells. This effect is mediated by ionotropic purinergic signaling in the breast cancer cells [21].

BM-MSCs have been shown to exert inhibitory effects on the proliferation of BM2 cells, as well as reduce stem cell-like surface protein expression, suppress their invasiveness through Matrigel Transwells, and decrease their sensitivity to docetaxel. These effects are attributed to the transfer of microRNAs (miRNAs) from BM-MSCs to BM2 cells via exosomes. BM-MSC-derived exosomes contain various miRNAs, including miR-23b, which could suppress the expression of MARCKS, a protein associated with metastatic cancers. The inhibition of MARCKS expression by miR-23b results in cell cycle arrest and dormancy of BM2 cells [15]. A study conducted by Lai et al. revealed that exosomes derived from MSCs contain all seven alpha

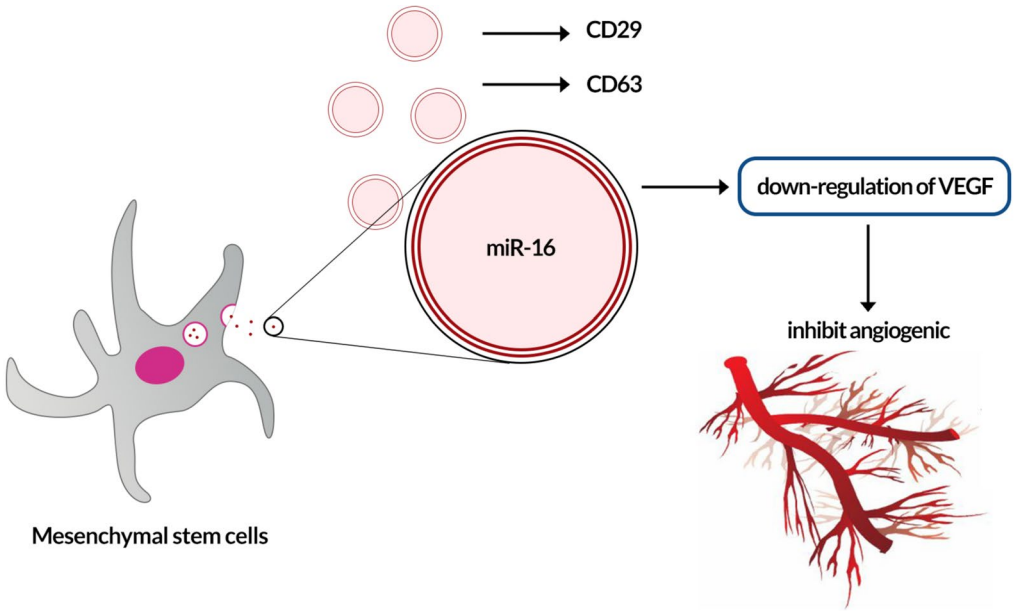

Fig. 2 Breast cancer cells uptake exosomes derived from MSCs which leads to a reduction in VEGF expression and results in the inhibition of angiogenesis. A significant factor present within these exosomes is miR-16, which plays a crucial role in downregulating VEGF expression specifically in breast cancer cell lines

and seven beta chains of the 20S proteasome, as well as the three beta subunits of the immunoproteasome. Consequently, these exosomes have the potential to influence tumor cells by transferring proteasomes [22]. Protein degradation in eukaryotic cells occurs through two main pathways: proteasome-mediated degradation and autophagy-lysosome degradation systems. The degradation of cellular components and organelles through autophagy involves the random transport of these structures to lysosomes for breakdown, unlike the targeted degradation seen in Ub-proteasome pathways. Proteasome-mediated degradation, however, occur upon the selective binding of the ubiquitin to the damaged protein. The damaged proteins are then broken down into 3–25 peptides by the 20S subunit of the proteasome, which exhibits peptidase activity [23].

The roles of fibroblast—derived exosome on cancer cell

Fibroblasts are a major constituent of connective tissue. Cancer-associated fibroblasts (CAF) are a unique subtype of fibroblast that actively participate in the growth and invasion of cancer cells. The close interaction between cancer cells and fibroblasts makes cancer-associated fibroblasts crucial in the progression of cancer, as these cells secrete a variety of factors that contribute to the development and progression of cancer cells [24].

The primary precursor of CAFs is normal fibroblasts, which are influenced by factors that are secreted by cancer cells, including transforming growth factor-β (TGF-β) [25]. In an animal model, a study has reported that CAFs can originate from bone marrow-derived cells or via the conversion of epithelial or endothelial cells into mesenchymal cells [26]. The exosomes derived from fibroblasts have been found to enhance the proliferative and invasive capacity of bladder cancer cells. This effect is attributed to the upregulation of LINC00355, a long intergenic non-coding RNA, within the exosomes [27]. A recent study conducted by Guang Shan et al. demonstrated that exosomes derived from CAFs can induce taxane resistance in prostate cancer cells. Specifically, the presence of miR-423-5p within CAF-derived exosomes was found to be a key contributor to this drug resistance. This effect is purportedly mediated by the suppression of GREM2 via the TGF-β signaling pathway [28].

Exosomes that are secreted by CAFs in human breast tissue promote mobility and metastasis in breast cancer cells. This effect is mediated by exosomal CD81, which is internalized by breast cancer cells, leading to the production of Wnt11. The impact of CD81 on breast cancer cells is attributed to its effect on the core of the planar cell polarity (PCP) pathway. Specifically, the exosomes cause a specific distribution of PCP components within breast cancer cells, which can affect various cellular behaviors and conditions [29]. The core PCP genes constitute a set of evolutionarily conserved genes that play crucial roles in establishing molecular asymmetry both within and between cells. These

genes include Frizzled, Flamingo, Van Gogh, Prickle, Disheveled, and Diego [30].

Exosomes derived from CAFs that contain miR-181d-5p have the ability to promote tumor growth by downregulating the expression of CDX2 and HOXA5. Additionally, miR-181d-5p has been found to exert anti-apoptotic and pro-proliferative effects on MCF-7 cells [31]. The expression of the HOXA5 gene is commonly downregulated in breast cancer, and this is often associated with adverse disease outcomes [32]. Exosomes that are derived from fibroblasts and contain cytokines, such as IL-6, Activin-A, and G-CSF, can affect gene expression through upregulation of STAT3 and Smad signaling pathways. These exosomes activate stemness-related signaling pathways, including Wnt, Notch, and Hedgehog, which can reprogram tumor cells. The effect of these exosomes is further sustained by the presence of Granulocyte colony-stimulating factor (G-CSF) [33].

In addition to the aforementioned functions of CAFs in driving cancer progression, these cells also play a significant role in promoting therapeutic resistance [34]. Exosomes derived from CAFs that contain microRNA-21 (miR-21) have been illustrated to influence ovarian cancer cells, resulting in increased resistance to the chemotherapy drug paclitaxel. This effect is thought to be mediated by the downregulation of the apoptotic protease activating factor 1 (APAF-1) gene [35]. The upregulation of miR-21 expression is a well-established phenomenon in the context of various types of malignant tumors, and is strongly associated with drug resistance [36] (Fig. 3).

By contrast, upregulation of exosomal microRNA-4516 (miR-4516) originating from CAFs was found to inhibit

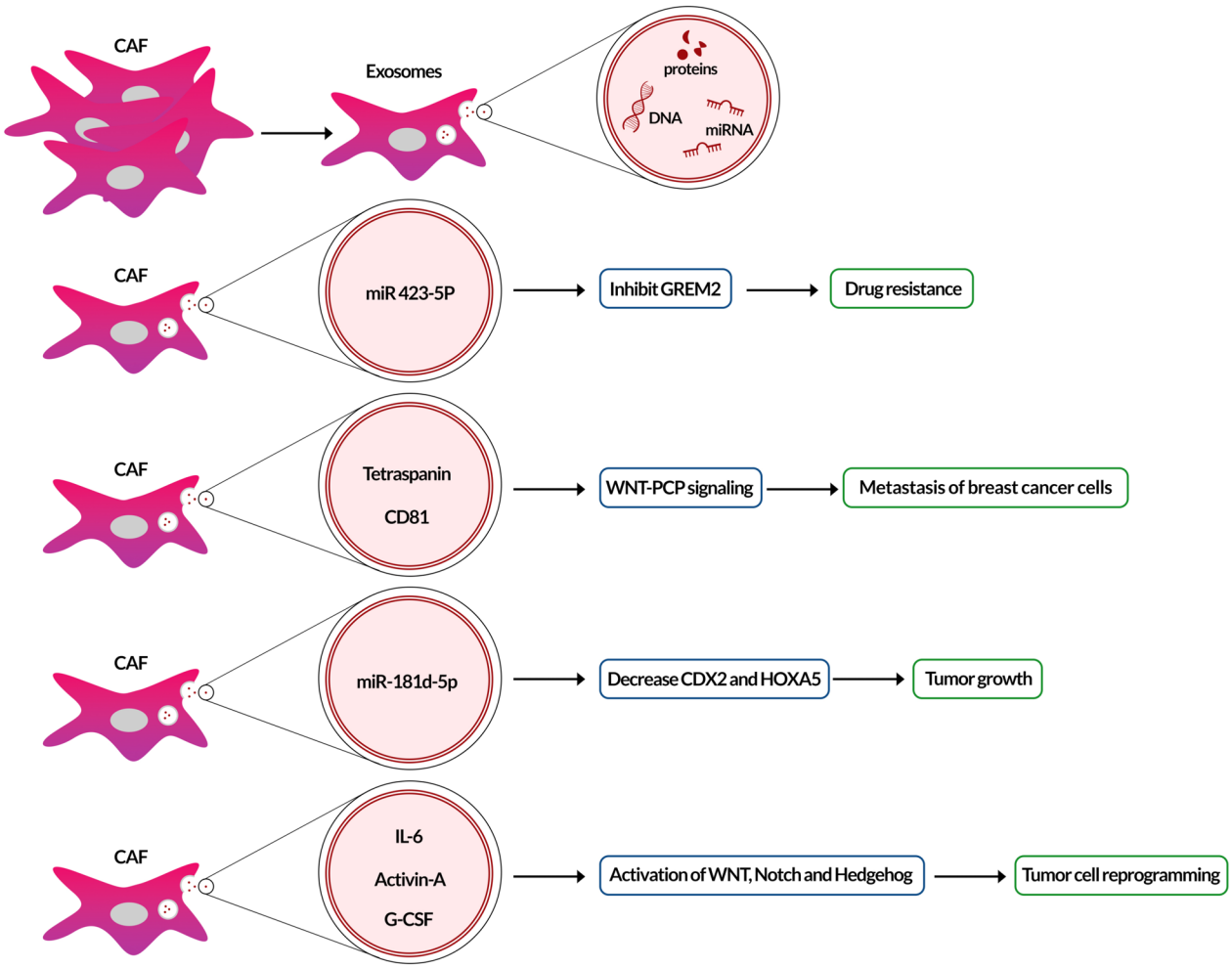

Fig. 3 Exosome derived fibroblast can enhance breast cancer metastasis and drug resistance through several distinct mechanisms which include GREM2 suppression through TGF-β signaling pathway, increase in WNT-PCP pathway signaling in tumor cells, CDX2 and HOXA5 downregulation and carrying IL-6, Actin A and G-CSF by upregulation of STAT3 and Smad pathways

the proliferation of breast cancer cells by modulating the expression of the FOSL1 gene. Indeed, the study revealed that miR-4516 and FOSL1 gene exhibited an inverse relationship with respect to the proliferation of cancer cells [37].

Studies have demonstrated that exosomes derived from CAFs can modulate cancer growth through the transfer of miR-590-3p. Specifically, miR-590-3p has been found to enhance radio resistance in colorectal cancer cells by activating the PI3K/Akt signaling pathway while concurrently inhibiting the expression of the CLCA4 gene [38]. The upregulation of microRNA-590-3p (miR-590-3p) in colon cancer cells triggers the activation of the Wnt/ß-catenin signaling pathway, which in turn leads to enhanced cell proliferation and increased tumorigenic potential of these cells [39]. Alternatively, exosomes secreted by CAFs containing miR-92a-3p drive a multitude of events in colon cancer cells which encompass the activation of the Wnt/β-catenin pathway, inhibition of mitochondrial apoptosis via the downregulation of FBXW7 and MOAP1, acquisition of cell stemness, induction of the epithelial-mesenchymal transition (EMT), promotion of metastasis, and resistance to 5-FU/L-OHP [40]. Exosomes containing miR-181d-5p, which are secreted by CAFs, could exert multiple effects on breast cancer cells. Specifically, these exosomes promote cancer cell proliferation, invasion, migration, epithelial-mesenchymal transition and anti-apoptosis by modulating the expression of CDX2 and HOXA5. CDX2 acts as a transcription factor that can influence the expression of HOXA5, and these two genes are positively correlated with each other [31]. On the other hand, exosomal microRNA-150-3p obtained from CAFs suppressed hepatocellular carcinoma cells, making it a potential candidate for antitumor therapy [41]. Similarly, another study indicating that exosomal miR-320a originating from CAFs can impede the advancement of hepatocellular carcinoma cells by acting on the PBX3-Erk1/2 signaling pathway. It is worth noting that PBX3 has the ability to activate the MAPK pathway, which is known to promote cell proliferation and metastasis via the induction of epithelial-mesenchymal transition, as well as the upregulation of cyclin-dependent kinase 2 and MMP2 [42]. The exosomal microRNA-3188 originating from CAFs impedes the progression of head and neck cancer by repressing the expression of BCL2. BCL2 is a member of the BCL2 family that is known for its anti-apoptotic properties and is frequently overexpressed in a variety of tumors [43].

According to another research, exosomal miR-148b that originates from CAFs possesses the ability to hinder the advancement of endometrial cancer cells by targeting the DNMT1 gene. DNMT1 is widely recognized as an oncogene and plays a critical part in various tumorigenic processes [44]. A recent study demonstrated that exosomal circSLC7A6, a subtype of circular RNA, originating from CAFs, may play a critical role in promoting tumorigenesis in colorectal cancer by modulating CXCR5 expression [45]. Table 1 summarized several CAF-originated MicroRNA and their roles in drug resistance in cancers.

The roles of adipocyte—derived exosome on cancer cell

The adipocyte is a crucial constituent of the tumor microenvironment that can significantly impact tumor progression. Cancer-associated adipocytes (CAAs) exhibit a strong association with cancer cells, not only those located in the immediate vicinity, but also those situated at a distance, by releasing a diverse array of components [55]. CAAs release exosomes that contain a wide variety of factors that modulate tumor cells. For instance, CAA-derived exosomes have been shown to enhance melanoma cell migration and invasion by transporting proteins associated with fatty acid oxidation. Research has demonstrated a correlation between obese melanoma patients and a worse prognosis, potentially due to the effects of CAA-derived exosomes on tumor progression [56]. Moreover, exosomes derived from cerebral amyloid angiopathy and enriched with matrix metallopeptidase 3 (MMP3) promote tumor cell invasion by activating MMP-9 in recipient cells. Specifically, MMP3-containing exosomes are transferred to lung tumor cells, resulting in the activation of MMP-9 protein [57]. MMP-9 is a crucial protease that is involved in a variety of biological processes. This protein plays a significant role in remodeling the extracellular matrix, which in turn, affects various aspects of tumor progression, including metastasis, invasion, and angiogenesis [58].

Microvesicles interactions with stromal and cancer cells

Microvesicles (MVs) form through direct budding from the plasma membrane and typically range in diameter from 100 to 1000 nm. These MVs contain a high concentration of phosphatidylserine and other lipid components. The production of MVs is regulated by the interplay between phospholipid redistribution and the contraction of cytoskeletal structure [59].

The majority of eukaryotic cells produce MVs either constitutively during early apoptosis or at increased amounts during chemical or physical stress conditions. MVs are involved in a variety of processes related to intercellular communication and signal transduction, such as membrane repair, the removal of misfolded proteins, mRNA and microRNA transport, protein

Table 1 MicroRNA and their roles in various type of cancers and their impact on cellular functions, signaling pathways and treatment resistance

Origin	MiRNA	Type of cancer	Target and pathway	Function	References
CAF	miR-21	Ovarian cancer cells	APAF-1	Increased ovarian cancer cell chemoresistance (paclitaxel) and had an anti-apoptotic effect on ovarian cancer cells	[46, 47]
	miR-21	Pancreatic ductal adenocarcinoma	Inhibit PDCD4 expression	Activate CAFs and resistant to gemcitabine treatment	[48]
	miR-21	Colorectal cancer	Tumor suppressors PTEN and PDCD4	Tumor progression and liver metastases	[49]
	miR-146a	Pancreatic ductal adenocarcinomas	Snail	Increased proliferation and chemoresistance of cancer cells	[50]
	miR-148b	Endometrial cancer cell	DNMT1	Decrease level of miR-148b result to endometrial cancer progress and cancer metastasis	[44]
	miR-196a	Head and neck cancer	CDKN1B / ING5	Head and neck cancer-resist to cisplatin treatment	[51]
	MiR-106b	Pancreatic cancer cells	TP53INP1	Resistant to Gemcitabine	[52]
	miR-339-5p	Esophageal squamous cell carcinoma	Downregulation of Cdc25A	Increase radio sensitivity of tumor cells	[48]
	miR-34a-5p	Oral squamous cell carcinoma	AKT/GSK-3β/β-catenin/Snail signaling	miR-34a-5p bind to AXL target and suppress oral squamous cell carcinoma tumorigenesis	[53]
	miR-17-5p	Colorectal cancer	RUNX3/MYC/TGF-β1 signaling	Activation of TGF-β1 led to tumor progression	[54]

transport (unconventional protein export), and apoptosis control. Moreover, MVs have been demonstrated to play a part in tumor hypoxia, invasive development, and metastasis [60].

In the tumor microenvironment, cancerous and stromal cells exchange information via MVs released by the malignant cells. These MVs have a significant impact on various tumor processes such as proliferation, apoptosis, angiogenesis, metastasis resistance to chemotherapy, and immune system modulation. The chemokines carried by these MVs could be essential for identifying predictive markers and enhancing effective treatment strategies [61].

According to reports, tumor-associated MVs are important in the process of fibroblasts differentiating into CAFs and creating a stroma that promotes tumor growth. Tumor-derived MVs can not only activate fibroblasts, but also differentiate mesenchymal stem cells and other bone marrow-derived cells into tumor-supportive cells by supplying growth factors like transforming growth factor-beta (TGF-β) and other miRNAs [62].

The MVs released by cancer cells have the ability to induce normal fibroblasts and epithelial cells to acquire the characteristics of cancer cells. The transfer of tissue transglutaminase (tTG), an enzyme that cross-links fibronectin (FN) proteins, is essential for this effect to occur. The MVs produced by cancer cells induce transformation by transferring tTG along with cross-linked FN to recipient fibroblasts through MVs. This collaborative action triggers mitogenic signaling pathways and leads to fibroblast transformation [63].

The research conducted by Asish et al. explored the correlation between MVs released by chronic lymphoblastic leukemia (CLL) cells and their impact on bone marrow stromal cells (BMSC). The study revealed that CLL-derived MVs can trigger the activation of the Phosphatidylinositol 3-kinase (PI3K)/AKT target of rapamycin/p70S6K/hypoxia-inducible factor-1α axis in CLL-BMSCs. This activation leads to the production of vascular endothelial growth factor (VEGF), a crucial survival factor for CLL-B cells. Additionally, the activation of AKT by MVs can stimulate the β-catenin pathway and increase the expression of cyclin D1 and c-myc in BMSCs. The researchers also observed that BMSCs received phospho-receptor tyrosine kinase Axl directly from MVs, along with AKT activation [64].

Cancer cells possess the capacity to release oncogenic EGFR in the form of membrane MVs, enabling interaction with the surfaces of neighboring cells. Endothelial cells in culture are capable of taking up MVs produced by human cancer cells containing active EGFR (A431, A549, DLD-1) and subsequently reacting to them by triggering EGFR-dependent pathways such as the MAPK and Akt pathways. Consequently, MVs

derived from tumor cells carrying oncogenes could serve as a unique type of angiogenesis-modulating signal, inducing endothelial cells to exhibit autocrine behavior [65].

Hypoxic cancer cells were found to release substantial levels of tissue factor (TF), primarily associated with secreted MVs exhibiting exosome-like characteristics. Research revealed that vesicles derived from glioma cells activate paracrine hypoxic endothelial cells in a TF/VIIa-dependent fashion. A study provided evidence of a hypoxia-induced signaling cascade linking PAR-2-mediated activation of endothelial cells to coagulation activation in cancer cells. Consequently, targeting this communication system during the development of treatments for invasive brain tumors may be of interest [66].

Cancer-derived apoptotic bodies impact on stromal cells

Apoptosis is a programmed cell death process that occurs naturally in living organisms, characterized by cell shrinkage, chromatin condensation, and plasma blebbing. Various biological processes, such as embryonic development and cell renewal, highlight the significance of apoptosis. Moreover, apoptotic cells can promote tissue regeneration by stimulating the growth of progenitor cells to replace damaged cells [67].

The interactions between apoptotic bodies and stromal cells can affect the behavior and functionality of stromal cells in tumors. These interactions may play a role in determining the progression of cancer and the outcomes for patients. Changes in gene expression patterns in stromal cells when exposed to apoptotic bodies could influence tumor growth, invasion, and metastasis. Understanding how stromal cells respond to apoptotic bodies can provide insights into the complex interactions among different cell types in the tumor microenvironment [68].

A research study has shown that apoptotic glioblastoma cells release apoptotic extracellular vesicles containing various spliceosome components, which paradoxically promote the growth and resistance to treatment of surviving tumor cells. The apoptotic extracellular vesicles alter the RNA splicing of recipient cells, leading to increased resistance to therapy and enhanced migratory behavior. The study also found that when apoptosis is triggered, a common splicing factor (RBM11) is released within extracellular vesicles. Upon uptake by recipient cells, the exogenous RBM11 induces splicing changes in MDM4 and Cyclin D1, resulting in the production of more oncogenic isoforms [69].

Adjacent viable cells in close proximity have the potential to produce apoptotic bodies that are derived from tumor endothelial cells. Research has shown that tumor DNA can be transmitted from apoptotic tumor cells to fibroblasts and endothelial cells, particularly when the apoptotic tumor cells contain the SV40 big T antigen. In an in vivo study, a specific group of endothelial cells carrying tumor DNA can form operational capillaries, all the while exhibiting genes associated with endothelial growth and tumor coding [70].

Further research has revealed that apoptotic bodies are involved in controlling the immune reaction to tumors. By triggering CD8 + T-cell activity and promoting regulatory T-cell responses via membrane-bound transforming growth factor-beta1 (TGF-β1), tumor apoptotic bodies could impede cytotoxic T lymphocyte (CTL) responses and reduce antitumor immune reactions [71].

Therefore, recent data indicate that apoptosis could potentially promote neoplastic advancement or lead to relapse after treatment through various pathways. Additionally, tumor growth is supported by immunomodulatory, anti-inflammatory, and trophic responses in the environment triggered by apoptosis [72].

Conclusion

Given the aforementioned functions of stromal cells and the impact of exosomes derived from these cells on various stages of cancer progression, it is crucial to investigate and impede the action of exosomes as a potential strategy for preventing cancer advancement.

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Author contributions
Study design was done by Mahsa Najafzadeh, Seyed Mehdi Sajjadi, and Ebrahim Kharazinejad. Data collection and literature search were done by Mahsa Najafzadeh, Seyed Mehdi Sajjadi, Sam Kharazi, Farzaneh Karimifard, and Ebrahim Kharazinejad. Data interpretation was done by Mahsa Najafzadeh, Seyed Mehdi Sajjadi, Sam Kharazi, Ebrahim Kharazinejad, and Hossein Safarpour. Manuscript preparation was done by Mahsa Najafzadeh, Seyed Mehdi Sajjadi, and Ebrahim Kharazinejad.

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Availability of data and materials
All data generated or analyzed during this study are included in this published article and its supplementary information files.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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