Gene Reports 29 (2022) 101672

Contents lists available at ScienceDirect

Gene Reports

journal homepage: www.elsevier.com/locate/genrep

Contributions and therapeutic potential of tumor-derived microRNAs containing exosomes to cancer progression

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ARTICLE INFO

Edited by Dominic Voon

Keywords:
Exosome
Exosomal microRNA
Cancer progression
Therapy

ABSTRACT

Exosomes are membrane-encapsulated vesicles found in a wide range of bodily fluids. They are key cell-to-cell communication mediators and biological process regulators. Growing data suggest that tumor cells communicate with other tumor cells and cells in the tumor microenvironment via exosomal microRNA (miRNA) release and transfer. More notably, exosomal miRNAs have been reported to function as signaling molecules in tumor progression, angiogenesis, metastasis, stemness, chemotherapeutic sensitivity, apoptosis, and immune evasion. Exosomes offer the several benefits over traditional delivery methods like lipid nanoparticles (LNPs), which makes them more considerable to be used as the carrier of therapeutic agents. Also, exosomal miRNAs could serve a predictive capability in several types of cancers. In this review, we emphasized recent advances in the functional significance of exosomal miRNAs in malignant cells' characteristics. Besides, we highlighted the clinical potential of exosomal miRNAs as biomarkers for cancer diagnosis and treatment.

1. Introduction

When eukaryotic cells are healthy as well as when they are ill, a variety of membranous vesicles are released. These membrane-derived extracellular vesicles (EVs), based on their size, may be divided into two categories: Microvesicles, which range in size from 100 to 1000 nm, are the more significant class of nanometer-sized vesicles, whereas exosomes, which range in size from 30 to 100 nm, are the smaller class (Widjaja et al., 2022). It is critical to remember that these membrane-bound vesicles vary significantly from apoptotic bodies, which are produced from cells going through programmed cell death, have a different biological origin and chemical makeup, and include fragments of cell nuclei (Akers et al., 2013). Exosomes are equipped with the capacity to transmit signals between cells due to their abundance of bioactive substances, including metabolites, proteins, lipids, and nucleic acids (Raposo and Stoorvogel, 2013). Exosomes have been studied in several bodily fluids, including bile, blood, breast milk, urine, cerebrospinal fluid, and saliva, indicating that exosomes have a variety of

Abbreviations: EVs, extracellular vesicles; TME, tumor microenvironment; miRNA and miR, microRNA; 3′-UTRs, 3′-untranslated regions; mRNAs, messenger RNAs; lncRNAs, long non-coding RNAs; circRNAs, circular RNAs; CAFs, cancer-associated fibroblasts; EMT, epithelial-mesenchymal transition; VEGF, vascular endothelial growth factor; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor β; bFGF, basic fibroblast growth factor; MMPs, matrix metalloproteinases; pri-miRNAs, primary miRNAs; pre-miRNAs, precursor miRNAs; RISC, RNA-induced silencing complex; HnRNP, heterogeneous nuclear ribonucleoprotein; nSMase2, neutral sphyngomyelinase 2; HCC, hepatocellular carcinoma; DKK3, Dickkopf 3; NSCLC, non-small-cell lung cancer; MDSCs, myeloid-derived suppressor cells; HMBOX1, homeobox containing 1; LNPs, lipid nanoparticles; SIRPα, signal regulatory protein alpha; HA, hyaluronic acid; DOX, doxorubicin.

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https://doi.org/10.1016/j.genrep.2022.101672
Received 16 July 2022; Received in revised form 20 August 2022; Accepted 24 August 2022
Available online 28 August 2022

functions in controlling physiological responses (Ha et al., 2016). Several studies from the last decades consider the involvement of exosomes in the induction and progression of cancer (Schorey and Bhatnagar, 2008; Zitvogel et al., 1999; Gao and Jiang, 2018). Exosomes have been shown to have specific roles in tumor initiation, development, metastasis, angiogenesis, and treatment resistance, making them one of the most significant elements in the tumor microenvironment (TME) (Wang et al., 2019a; Moghadasi et al., 2021). Exosome-related growth factors and cytokines have the potential to activate or inhibit immune cells and lymphoid components of the TME, such as B and T lymphocytes, natural killer cells, and macrophages, which might lead to immunosuppression and tumor development (Yang et al., 2020).

The small (19–24 nt) non-coding RNAs known as microRNAs (miRNAs) control gene expression post-transcriptionally by directly interacting with the corresponding messenger RNA targets' 3′ untranslated regions (UTRs) (Sheervalilou et al., 2016; Mohammadian et al., 2017). The expression of miRNAs is dysregulated, which significantly impacts many biological functions, including cell proliferation, apoptosis, survival, invasion, metastasis, and chemotherapeutic resistance (Di Leva et al., 2014; Mohammadian et al., 2016a). Circulating miRNAs, which can resist RNase destruction and several freeze-thaw cycles, may be found in the blood in the form of Ago2-miRNA protein complexes (Norouzi et al., 2019; Mohammadian et al., 2016b). Due to their roles in enlisting and reprogramming crucial elements of the TME, miRNAs in exosomes are now receiving more and more attention. They are also thought to be crucial for transmitting soluble molecules that occur during cell-to-cell contact and intercellular communication (Fasken et al., 2020). This is an emerging idea with little knowledge about exosomal miRNAs in general. Therefore, we decided to thoroughly examine the impact of these extracellular agents on the development and spread of cancer in the present study.

2. Exosome biogenesis

Small membranous vesicles known as EVs may engage in intercellular communication between cells and are released from various cells into the extracellular matrix (ECM) (Balaphas et al., 2019). Apoptotic bodies (500 nm–5 m) produced during programmed cell death, microvesicles (150–500 nm) from the budding of the plasma membrane, and exosomes (40–150 nm) from endosomes are the three subgroups of EVs based on size and origin (Bunggulawa et al., 2018). Exosomes are released by many distinct cell types, such as cancer cells, dendritic cells, B cells, T cells, mast cells, and epithelial cells. They may be found in various bodily fluids, including blood, urine, malignant effusions, bronchoalveolar lavage fluid, breast milk, and others (Vlassov et al., 2012; Azmi et al., 2013). In vitro-cultured sheep erythrocytes' supernatant was where they were initially discovered in 1983 (Harding and Stahl, 1983; Pan and Johnstone, 1983). Exosomes were formerly thought of as cells' "Garbage Bags," used to remove waste materials from the cells. However, people later discovered that they were created by the invagination of the plasma membrane, followed by acidification and the maturation of mass exchange into the late endosomes. Exosomes are formed when late endosomes finally split into several vesicles whose membranes sprout intraluminal vesicles. They are finally secreted outside the cell by fusing the plasma membrane (Mathivanan et al., 2010). To facilitate intercellular communication, exosomes carry cellular and molecular components such as proteins, DNA, lipids, messenger RNAs (mRNAs), miRNAs, long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs). Data from the ExoCarta database (http://www.exocarta.org) show that 9769 proteins, 3408 mRNAs, 2838 miRNAs, and 1116 lipids have been shown to be present in identified exosome contents (Théry, 2011).

According to several pieces of research, exosomes have been shown to serve several purposes in malignancies. First, the exosomes' contents influence interactions between tumor cells and the TME, endothelial cells, fibroblasts, and invading immune cells (Kohlhapp et al., 2015). Second, exosomes control the TME and ECM by activating extracellular receptor signals and inhibiting cell adhesion (Luga et al., 2012; Sung et al., 2015). Exosomal integrins, for instance, contribute to the early colonization of cancer cells and the development of a pre-metastatic microenvironment (Paolillo and Schinelli, 2017). Third, exosomes from cancer cells may cause TME cells to differentiate into cancer-associated fibroblasts (CAFs), which comprise most of the TME cell population in most malignancies (Webber et al., 2010). Fourth, exosomes may also stimulate epithelial to mesenchymal transition (EMT), which favors the mobility and spread of tumor cells (Syn et al., 2016; Hussein et al., 2022). Finally, exosomes are connected to one of the primary processes causing angiogenesis. Vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), transforming growth factor β (TGF-β), and basic fibroblast growth factor (bFGF) are only a few of the angiogenic stimulatory substances that are carried by exosomes (Katoh, 2013; Vakili-Samiani et al., 2021). Endothelial cells are also reprogrammed and modulated by exosomes to promote angiogenesis (Ludwig et al., 2018).

Additionally, it has been stated that exosomes play a crucial role in every aspect of EMT, from the invasive phenotype to distant metastases (Whiteside, 2017). For example, exosomes containing matrix metalloproteinase (MMP) 13 encourage metastasis in nasopharyngeal cancer cells via EMT (You et al., 2015). By boosting the expressions of mesenchymal biomarkers like Smooth muscle alpha-actin (α-SMA), S100 Calcium Binding Protein A4 (S100A4), and snail and reducing the expressions of epithelial biomarkers like E-cadherin and β-catenin, exosomes produced by bladder cancer cells may induce EMT in urothelial cells (Franzen et al., 2015). Exosomes also contribute significantly to the chemoresistance of malignancies. Tum cells may use exosomes to transport chemotherapy medicines away (Safaei et al., 2005). Exosome carrying capacity is linked to tumor medication resistance (Shedden et al., 2003). Exosomes produced by tumors may limit immune effector cells' ability to respond and activate immune suppressor cells, which makes malignancies more resistant to chemotherapy (Hellwinkel et al., 2015). Additionally, exosomes may act as a ruse to assist cancer cells in eluding immune effector cells (Battke et al., 2011).

3. Exosomal miRNAs, mechanism, and function

Exosomes contain a variety of RNA molecules, the majority of which are non-coding RNAs, such as lncRNAs, circRNAs, and miRNAs. Of these, miRNAs have attracted the most attention because they have the highest content and are crucial in regulating gene expression (Tan et al., 2020). Twenty-two nt endogenous non-coding short RNAs known as miRNAs have a role in translational repression or mRNA turnover to decrease gene expression. By attaching to the 3'-UTR of mRNAs, miRNAs may target them for cleavage or prevent their translation, therefore suppressing the expression of the targeted genes (Bartel, 2004). The nuclear compartment is the starting point of the biogenetic process that results in exosomal miRNAs, where DNA sequences that produce miRNAs are translated by RNA polymerase to produce primary miRNAs (pri-miRNAs). The produced pri-miRNAs are first a part of larger molecules and are then transformed into 70–100 nt long hairpin RNAs in the nucleus (Fan et al., 2020). Hairpin pri-miRNAs are transported by Exportin 5 to the cytoplasm, where Dicer continues the processing. These double-stranded miRNAs undergo strand-splitting during maturation, followed by miRNA sorting into exosomes (Li et al., 2022a). Selective sorting determines the kind and quantity of miRNA contained in exosomes. Even though the regulation mechanism is not entirely known, mounting evidence suggests that miRNAs may be organized along one of four pathways: (1) A method reliant on the heterogeneous nuclear ribonucleoprotein (HnRNP) and the miRNA motif. The common short sequence GGAG (also known as the "EXO sequence"), which is found chiefly at the 3′-terminal of miRNAs and may bind specifically to hnRNPA2B to be included in exosomes, is found in miRNAs that have been loaded into exosomes (Villarroya-Beltri et al., 2013). (2) A method relying on

neutral sphyngomyelinase 2 (nSMase2). Exosomal miRNA concentration rises when nSMase2 is overexpressed and vice versa (Kosaka et al., 2013). (3) the route connected to the Y-box protein 1 (YBX1) (Shurtleff et al., 2016). (4) A route reliant on the 3′ end miRNA sequence. While 3′ end uridylated isoforms are comparatively abundant in exosomes, 3′ end adenylated miRNAs are primarily found in cells, which implies that 3′ end miRNAs may carry significant sorting signals (Koppers-Lalic et al., 2014). Exosomes may transport metabolites and facilitate cell-to-cell contact via the interchange of exosomal miRNAs. They then play a role in the immune response, modification of the TME, and tumor metastasis as the tumor progresses (Wu and Liu, 2018). Numerous studies suggest that exosomes transport miRNAs from donor cells to recipient cells, which alters the biology of the recipient cells, however the process by which exosomes sort miRNAs remains a mystery. The most recent version of the exosomes database (www.exocarta.org) lists 2838 miRNAs. 593 miRNAs have been found in exosomes out of the 2588 identified miRNAs in the human genome (Schwarzenbach and Gahan, 2019).

Primary tumor-derived exosomal miRNAs may be transmitted to non-cancerous cells throughout the TME to cause heterogeneity (Xu et al., 2018; Gao et al., 2020). Non-malignant cells may potentially leak exosomal miRNAs to control further tumor cells or other microenvironmental elements simultaneously as their biological activity changes in the TME (Sun et al., 2018). Cancer-associated fibroblasts (CAFs), endothelial cells, and immune cells are often the stromal cell receptors of cancer-derived exosomal miRNAs in TME. Exosomal miRNAs' influence on the heterogeneity of the TME is mainly shown in their ability to activate cancer-associated fibroblasts and modify the ECM, which is helpful for the growth of tumor cells (Bell and Taylor, 2017). In addition, exosomal miRNAs encourage the production of tubes in endothelial cells, and the development of many vascular networks is beneficial for the metabolism and survival of tumor cells. Exosomal miRNAs also play a role in immune evasion and inflammatory cell infiltration, which helps tumor cells colonize and grow. Exosomal miRNAs can improve TME's suitability for tumor formation via these macroscopic effects (Salehi and Sharifi, 2018).

4. Exosomal miRNAs in cancer progression

Exosomal miRNAs could considerably affect several aspects of cancer progression (Fig. 1). Below are some of the most important involved aspects.

4.1. Angiogenesis and metastasis

Angiogenesis is the process of creating new blood vessels from the vasculature that already exists. It entails the following sequential processes, beginning with perivascular detachment, moving on to vascular dilatation, angiogenic sprouting, the creation of new vessels, and lastly, the recruitment of perivascular cells for neovessel stabilization (Tonini et al., 2003; Maashi et al., 2022). Numerous studies in various cancer types have shown the significance of tumor-derived exosomal miRNAs in stimulating angiogenesis, which in turn supports tumor development and metastasis. Exosomal miR-210 produced by hepatocellular carcinoma (HCC) cells may enter endothelial cells and promote tumor angiogenesis by targeting Mothers against decapentaplegic homolog 4 (SMAD4) and Signal transducer and activator of transcription 6 (STAT6) (Lin et al., 2018). It has also been shown that exosomal miR-378b, produced from HCC cells, promotes angiogenesis and HCC cell growth and may be related to Transforming growth factor beta receptor III (TGFBR3) (Chen et al., 2021). The co-culture of HUVECs and exosomes produced by gastric cancer cells boosted angiogenesis, as seen by the increased production of Vascular endothelial growth factor (VEGF) but reduced expression of Thrombospondin 1 (TSP-1). Phosphatase and tensin homolog (PTEN), which had a low expression in gastric cancer tissues, was targeted by miR-23a. Exosomes generated from gastric cancer cells contained miR-23a, which in a co-culture system enhanced angiogenesis by suppressing PTEN (Du et al., 2020). Recent research has shown that the exosome route allows miR-141, abundantly expressed in lung cancer cells, to penetrate tumor stromal vascular endothelial cells. By focusing on the expression of growth arrest-specific homeobox (GAX), miR-141 promotes angiogenesis and the malignant development of tumors (Wang et al., 2021a). Exosomal miR-301a-3p, secreted by esophageal squamous cell carcinoma cells, is also shown to cause M2 macrophage polarization by inhibiting PTEN expression and activating the Phosphoinositide 3-kinases (PI3K)/AKT signaling pathway. This, in

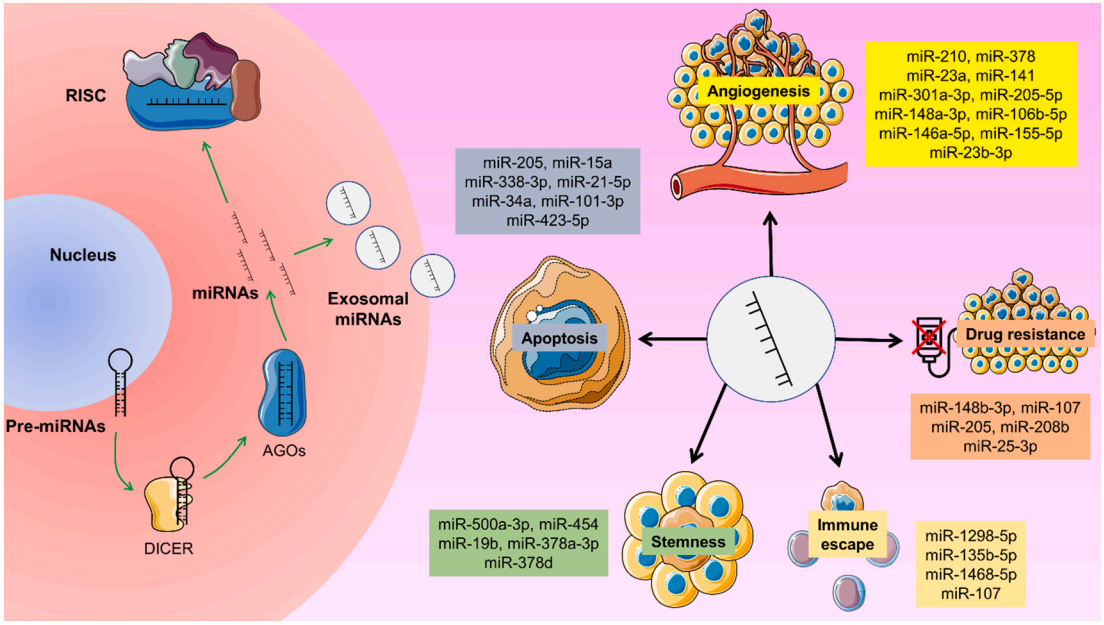

Fig. 1. Exosomal miRNAs in cancer progression. After the biogenesis of miRNAs within a cell, these exosomes are released via exocytosis. Exosomal miRNAs can affect angiogenesis, drug resistance, immune escape, stemness, and inhibited apoptosis of malignant cells.

turn, causes the secretion of the angiogenic factors VEGFA and MMP9, which in turn promotes angiogenesis (Shou et al., 2022). According to Yang et al., exosomal miR-205-5p targets DSC2 to boost Epidermal growth factor receptor (EGFR)/ERK signaling and MMP production, which in turn promotes angiogenesis and nasopharyngeal cancer metastasis (Yang et al., 2022). Exosomal miR-148a-3p, produced from glioma cells, was shown to downregulate ERRFI1 and activate the EGFR/MAPK signaling pathway in the glioma, promoting cell proliferation and angiogenesis (Wang et al., 2020). According to reports, exosomal miR-106b-5p, produced from tumors that undergo epithelial-mesenchymal transition (EMT), encourages macrophages to polarize in an M2-like manner by suppressing Programmed Cell Death 4 (PDCD4) and activating the PI3Kγ/AKT/mTOR signaling pathway. By encouraging the EMT of tumor cells in a feedback way, activated macrophages allow the intravasation of tumor cells to mediate the production of circulating tumor cells, hence increasing the liver and lung metastases of colorectal cancer (Yang et al., 2021a). Furthermore, Wang et al. discovered that the CXCL12/CXCR7 axis activation boosted exosomal miR-146a-5p and miR-155-5p to promote CAF activation, which changes the secretory phenotype of Cancer-associated fibroblasts and encourages EMT and metastasis of colorectal cancer (Wang et al., 2022). Exosomal miR-23b-3p's impact on the development of salivary adenoid cystic carcinoma was examined by Hou et al. Exosomal miR-23b-3p increased vascular permeability and decreased the expression of tight junction proteins, according to in vitro research. Exosomal miR-23b-3p also promoted migration and angiogenesis (Jalil et al., 2022; Hou et al., 2022).

4.2. Stemness

Over the last several years, a plethora of research has shown that the overexpression or downregulation of various exosomal miRNAs in malignancies may modulate stemness to support cancer formation. For example, it has been shown that gastric cancer cells may secrete exosomes that are high in miR-500a-3p in order to increase stemness by targeting FBXW7. Additionally, it was shown that overexpression of FBXW7 inhibited the characteristics of CSCs that were produced by exosomal miR-500a-3p (Lin et al., 2020). Wang and colleagues researched to investigate the function of the exosomal miR-454 generated by MDA-MB-231 in the self-renewal of cancer stem cells in ovarian cancer. It has been shown that exosomes produced from MDA-MB-231 cells may disrupt the Wnt pathway to target PRRT2, which in turn can promote the stemness of cancer stem cells (Gao et al., 2020). A recent study showed that exosomal miR-19b derived from colorectal cancer cells resulted in the maintenance of stemness and radioresistance of colorectal cancer cells. This was accomplished by downregulating FBXW7 expression and inducing the Wnt/β-catenin pathway. This suggests that miR-19b inhibition could be a potential target for the diagnosis and treatment of colorectal cancer (Sun et al., 2022). In response to stimulation with doxorubicin or paclitaxel, exosomes formed by breast cancer cells transfer miR-378a-3p and miR-378d to surrounding cells. These exosomes activate the WNT and NOTCH stemness pathways and cause drug resistance by targeting Dickkopf 3 (DKK3) and NUMB (Yang et al., 2021b). In addition, it was revealed that HCC cells generated exosomes enhanced resistance of HCC cells to sorafenib treatment and upregulated stemness-related signatures (OCT4, Nanog, SOX2, and ALDH1), which were all abrogated by treating anti-PD-L1 antibody. This suggests that HCC cells derived PD-L1 exosomes self-regulated cell stemness from increasing resistance of HCC cells to sorafenib (Zhao et al., 2021a).

4.3. Inhibited apoptosis

As previously indicated, exosomal miRNAs may affect cancer development in various ways, including controlling cell death. miR-205 may function as a proto-oncogene in the development of ovarian cancer, according to recent research. Exosomes from donor ovarian cancer cell SKOV3 that carried miR-205 might influence receptor SKOV3 cells' ability to apoptosis via controlling VEGFA, making miR-205 an ovarian cancer diagnostic biomarker with potential (Wang et al., 2019b). Additionally, mesenchymal stem cell-derived exosomes transfer miR-15a to HCC cells to suppress the proliferative, migratory, and invasive potentials of HCC cells while promoting death (Ma et al., 2021). According to Tian et al., increased CHL1 expression accelerates the growth of non-small-cell lung cancer (NSCLC) cells by encouraging their proliferation and stifling their apoptosis.

On the other hand, the downregulation of the CHL1 gene slowed the proliferation of NSCLC cells and increased the apoptosis rate of tumor cells. CHL1 also stimulated the MAPK signaling pathway. Additionally, it has been shown that miR-338-3p directly sponged with CHL1 to control the growth of tumor cells. Low blood levels of exosomal miR-338-3p were seen in NSCLC patients. Furthermore, by inhibiting the activation of the MAPK signaling pathway, higher exosomal miR-338-3p levels significantly reduced tumor cells' ability to proliferate and facilitated their death (Tian et al., 2021). Apoptosis in ovarian cancer cells was brought on by miR-21-5p inhibitor.

Furthermore, miR-21-5p inhibitor might downregulate the expression of anti-apoptotic Bcl2 while upregulating the expression of pro-apoptotic cleaved caspase3 and Bax in the cells (Cao et al., 2021). In colorectal cancer, miR-34a functions as a master tumor suppressor and may control many genes involved in tumor invasion, proliferation, immune evasion, and progression. The apoptosis and tumor growth of colorectal cancer cells are reportedly promoted and inhibited by tumor-derived exosomes carrying miR-34a (Hosseini et al., 2021). Xue et al. discovered that in exosomes isolated from the plasma of medulloblastoma patients, 35 miRNAs were elevated and five downregulated compared to healthy controls. In addition, they discovered that in an extended cohort, the expression of miR-101-3p and miR-423-5p was noticeably greater in plasma exosomes from medulloblastoma patients compared to healthy controls and that these exosomal miRNAs could be transported to tumor cells through exosomes. A substantial reduction in tumor cell proliferation and an increase in cell death were seen in medulloblastoma cells treated with the matching mimics, according to an in vitro functional investigation of miR-101-3p and miR-423-5p (Xue et al., 2022).

4.4. Drug resistance

Drug resistance has many causes, but the ones that are now understood include drug efflux, drug target mutation, metabolic drug changes, DNA damage repair, changes in energy programming, cancer stem cells, and epigenetic modifications. Exosomal miRNA controlled the majority of these functions (Guo et al., 2020). Exosomes from cancer-associated fibroblasts and exosomal miR-148b-3p have been discovered to increase metastasis and treatment resistance in bladder cancer cells. However, their effects may be reversed by upregulating the Wnt/β-catenin pathway and overexpressing PTEN (Shan et al., 2021). Additionally, recent research on the impact of exosomal miR-107 on chemotherapeutic drug resistance discovered that resistant gastric cancer cells might become more sensitive to exosomal miR-107 when retrieved from sensitive gastric cancer cells. They also discovered that HMGA2, a minor non-histone nuclear protein, and a transcription factor called the framework were the target molecules of exosomal miR-107. Their findings demonstrated that exosomal miR-107's ability to reverse resistant gastric cancer was mediated by controlling the expression of the target gene HMGA2, the activity of the mTOR pathway, and the expression of P-gp (Jiang et al., 2021).

Furthermore, it has been shown that exosomal miR-205 directly binds to E2F1 and that overexpressing E2F1 might counteract miR-205's impact on carcinogenesis and chemoresistance in breast cancer cells (Zhao et al., 2021b). In colon cancer, tumor cells produced exosomal miR-208b in the pattern of exosomes, and oxaliplatin-resistant cells had

the most pronounced rise in miR-208b. miR-208b released by colon cancer cells was adequately transported into recipient T cells to encourage Treg growth by targeting PDCD4. Additionally, it has been shown that oxaliplatin resistance and tumor development were caused by Treg expansion mediated by cancer cell-secreted miR-208b (Ning et al., 2021). Exosomal miRNA25-3p overexpression promoted the growth and temozolomide resistance of glioblastoma cells susceptible to the drug. It was discovered that miRNA253p directly targets FBXW7. Glioblastoma cells were more prone to proliferate and become resistant to temozolomide when FBXW7 was knocked down. Additionally, miR-25-3p exosomal transfer enhanced c-Myc and cyclin E expression by suppressing FBXW7 (Wang et al., 2021b).

4.5. Immune cells modulation and tumor escape

Exosomes produced by tumors include immunosuppressive substances that inhibit immune cells' ability to fight tumors. Immunologically active exosomes are secreted by immune and tumor cells alike and have an impact on intercellular communication, antigen presentation, immune cell activation, and immune surveillance (Olejarz et al., 2020). The control of critical immunological processes, including the formation, lineage commitment, activation, function, and aging of innate and adaptive immune cells, has been linked to an extensive array of miRNAs in recent years. For example, Exosomal miR-1298-5p has been shown to enable glioma by enhancing the immunosuppressive properties of myeloid-derived suppressor cells (MDSCs) (Qi et al., 2022). Exosomes produced by gastric cancer cells were discovered to be efficiently absorbed by γδ T cells, diminish the survival of these cells, cause apoptosis, and decrease the production of the deadly cytokines IFN-γ and TNF-α. Exosomal miR-135b-5p, which targets specificity protein 1, reduced the function of γδ T cells (SP1). More notably, the impact of persistent miR-135b-5p knockdown gastric cancer cell-derived exosomes on γδ T cell activity was eliminated by limiting the SP1 function with the SP1 inhibitor plicamycin (Li et al., 2022b).

Furthermore, Zhou et al. presented a mechanistic model in which exosome-encapsulated miR-1468-5p produced by cervical cancer stimulates lymphatic PD-L1 transcription and lymphangiogenesis to suppress T cell immunity. Exosomal miR-1468-5p directly targets homeobox containing 1 (HMBOX1) in the SOCS1 promoter, epigenetically activating the JAK2/STAT3 pathway in lymphatic endothelial cells triggering an immunosuppressive program that enables cancer cells to evade anti-cancer immunity (Zhou et al., 2021). Exosomes released by gastric cancer may carry miR-107 to the host MDSCs. Research has shown that this miRNA can enhance MDSC proliferation and activate its immunosuppressive role by upregulating ARG1 expression in MDSCs by downregulating the DICER1 and PTEN genes in these cells (Ren et al., 2019).

5. The therapeutic applications and prognostic value

Despite miRNAs' durability in extracellular fluids, their incorporation as a successful therapeutic agent has proven difficult (Baumann and Winkler, 2014). The delivery mechanisms and limited penetration to the target location of new miRNA therapies provide a significant issue. To address this issue, many molecular transporters have been developed and put to the test for successful miRNA and drug delivery. They consist of polymers, conjugation with sugars, lipids, and proteins, liposomes, exosomes, viral vectors, and conjugation with sugars (Segal and Slack, 2020; Mohandesnezhad et al., 2020; Firouzi-Amandi et al., 2018; Mousazadeh et al., 2021). However, regardless of the techniques employed to distribute miRNAs, they often interact with the acidic endosomal contents inside the cell, leading to their destruction by nucleases and complicating matters further. The use of pH-sensitive polyplexes, lipoplexes, and photosensitive molecules has been used in various endosome escape methods (Linsley and Wu, 2017; Saleh et al., 2022; Honarvari et al., 2022). Exosomes offer the following benefits over traditional delivery methods like lipid nanoparticles (LNPs): exosomes are more stable in bodily fluid than LNPs, while LNPs are simply eliminated by macrophages or reticuloendothelial cells (Soltani et al., 2015). In addition, exosomes have low cytotoxicity and immunogenicity due to their endogenous source and outstanding biocompatibility (Kim et al., 2021).

Additionally, since pharmaceuticals are contained inside the double-layer exosomal membrane rather than outside the LNPs, which are more easily degraded, exosomes may provide superior drug protection during delivery (Kim et al., 2020). These tiny carriers can transport chemicals that are both hydrophobic and hydrophilic. Additionally, they can effectively locate tumor locations due to their multivalent presentation of surface moieties originating from cells (Kim et al., 2021). Through the binding of CD47 on the exosomal surface and signal regulatory protein alpha (SIRPα) on the face of macrophages, exosomes originating from tumors may evade the phagocytosis of the mononuclear phagocyte system and send out a “do not eat me” signal (Pan et al., 2021). Due to their tiny size and unique properties, these vesicles may pass across the blood-brain barrier and reach the brain tissue (Li et al., 2017). Due to membrane proteins like tetraspanin and fibronectin, exosomes have rapid cellular absorption and are quickly changed to fit the target cells (Kim et al., 2021). By focusing on the HA receptor, which is overexpressed in breast cancer, it has been shown that hyaluronic acid (HA)-chitosan nanoparticles delivered tumor suppressor miR-34a and doxorubicin (DOX) to triple-negative breast cancer cells in vitro and in vivo (Deng et al., 2014)-reducing the anti-apoptotic proto-oncogene Bcl-2 and concentrating on Notch-1 signaling this reduced tumor development. Like this, miR-542 and DOX were effectively supplied by HA-coated polyethyleneimine-poly(d,ʟ-lactide-*co*-glycolide) nanoparticles, with enhanced targeting and more excellent absorption (Wang et al., 2016). In a different investigation, exosomes conjugated to the epidermal growth factor (EGF) peptide were used to encapsulate let-7a and target breast cancer cells that express the EGFR. Inhibiting mouse tumor development was achieved by delivering this miR through exosomes coupled with the synthetic peptide GE11 (Ohno et al., 2013).

Exosomal miRNAs' predictive capabilities in various cancer types have also been studied. Exosomal miR-200b and miR-200c serum levels can distinguish between benign and malignant EOC. 146 Exosomal miR-200b and miR-200c upregulation is associated with tumor growth and a reduced chance of survival in EOC patients. The exosomal miR-638 was reduced in the sera of HCC patients (Shi et al., 2018). The development of HCC was adversely linked with serum exosomal miR-638. HCC patients' downregulation indicated a dismal prognosis and low overall survival. Potentially, serum exosomal miR-638 might be a circulating biomarker for HCC. Exosomal miR-4772-3p may be able to distinguish between recurrent and non-recurrent colon cancer patients (Liu et al., 2016). A predictive biomarker for colon cancer patients with tumor recurrence may be exosomal miR-4772-3p. Poor outcomes in individuals with multiple myeloma were substantially linked with exosomal miR-let-7b and miR-18a levels (Manier et al., 2017). There was a correlation between miR-let-7i-5p, miR-26a-1-3p, and miR-615-3p and overall survival in patients with metastatic RCC. Exosomal miRNAs may serve as non-invasive indicators for cancer prognosis (Ansari et al., 2022; Du et al., 2017).

An early cancer diagnosis must increase the survival rate of cancer patients. Therefore, it is crucial to find efficient biomarkers (Zavari-Nematabad et al., 2017). Unfortunately, the sensitivity, specificity, and accuracy of blood-based cancer diagnostic indicators such as carcinoembryonic antigen (CEA) and -fetoprotein (AFP) are currently insufficient (Chatran et al., 2018; Lu et al., 2017; Marofi et al., 2021). Exosomal miRNAs have a significant potential as accurate cancer biomarkers because of their high stability, accessibility, and widespread distribution in bodily fluids. However, large-scale investigations are needed to identify the potential clinical value of exosomal miRNAs more clearly as diagnostic and prognostic biomarkers in cancer. In addition, exosomal miRNA expression levels are correlated with tumor type,

stage, and other clinical factors. As a result, it is crucial to establish the spectrum of exosomal miRNAs used and determine how they relate to common cancer indicators.

Furthermore, there are no defined methods for the isolation and identification of exosomes. It is still necessary to build a collection of reliable inner reference genes to precisely measure exosomal miRNAs. Before exosomal miRNAs may be used in therapeutic settings, these issues must be resolved.

6. Conclusion and future direction

Overall, the current review considered the biogenesis of exosomal miRNAs and their roles in cancer progression, including angiogenesis, stemness, inhibited apoptosis, drug resistance, and immune escape, as shown in Table 1. Also, the probable ability of this kind of miRNAs in cancer treatment was reviewed briefly. The two most crucial characteristics of tumor cells are growth and invasion. Tumor-promoting exosomes can accelerate glycolysis and cell cycle progression while inhibiting apoptosis. It is unclear what autophagy does. It has been stated that exosome-induced autophagy can stop cancer cells from apoptosizing. Therefore, further research should be done to understand how exosome-affected cancer cells interact with apoptosis and autophagy. Similar to how exosome cargo affects proliferation, exosome cargo also affects how well these structures facilitate cancer migration and invasion. Exosomes have a significant impact on EMT and MMPs in controlling the development of cancer. However, because MMPs play such a significant role in this situation, and because the majority of researchers have concentrated on the EMT process, it is suggested to investigate the signaling networks impacted by exosomes in targeting MMPs and influencing cancer metastasis. Response to therapy is influenced by cancer cell invasion and proliferation rates. Cancer cells may become resistant to treatment if they have a strong potential for migration and growth. Therefore, cancer cell invasion and proliferation may be controlled, and treatment outcomes can be anticipated by targeting exosomes. Interactions within the TME mostly influence cancer cell aggression. The interaction in the TME that is most recognized is macrophage polarization, which is mediated by exosomes. Exosomes can cause macrophages to become M2 polarized, accelerating the growth of cancer cells.

We have included a section that especially discusses the function of exosomes in this situation because responsiveness to medication is a significant issue for medical professionals treating cancer patients. Exosomes can lessen the susceptibility of cancer cells to chemotherapy-mediated apoptosis. Exosomes can transmit various genes, which means

Table 1
Exosomal miRNAs and their roles in several cancers.

Exosomal miRNA	Target	Type of cancer	Function	Ref
miR-210	SMAD4 and STAT6	Hepatocellular carcinoma	Promotes tumor angiogenesis.	(Lin et al., 2018)
miR-378b	TGFBR3	Hepatocellular carcinoma	Enhances progression and angiogenesis.	(Chen et al., 2021)
miR-23a	PTEN	Gastric cancer	Promotes the development of cancer by inducing angiogenesis.	(Du et al., 2020)
miR-141	GAX	Lung cancer	Promotes migration and invasion and tube formation.	(Wang et al., 2021a)
miR-301a-3p	PTEN	Esophageal squamous cell carcinoma	Promotes angiogenesis by inducing M2 polarization of macrophages	(Shou et al., 2022)
miR-205-5p	Desmocollin-2	Nasopharyngeal carcinoma	Promotes angiogenesis and metastasis	(Yang et al., 2022)
miR-148a-3p	ERRFI1	Glioma	Promotes cell proliferation and angiogenesis	(Wang et al., 2020)
miR-106b-5p	PDCD4	Colorectal cancer	Activates EMT-cancer cell and M2-subtype TAM interaction to facilitate metastasis.	(Yang et al., 2021a)
miR-146a-5p, miR-155-5p	SOCS1 and ZBTB2	Colorectal cancer	Facilitate distant metastasis.	(Wang et al., 2022)
miR-23b-3p	PTEN	Salivary adenoid cystic carcinoma	Promotes tumor angiogenesis and metastasis	(Hou et al., 2022)
miR-500a-3p	FBXW7	Gastric cancer	Promotes stemness properties.	(Lin et al., 2020)
miR-454	PRRT2	Breast cancer	Increases cancer stem cell stemness.	(Gao et al., 2020)
miR-19b	FBXW7	Colorectal cancer	Promotes stemness.	(Sun et al., 2022)
miR-378a-3p and miR-378d	DKK3 and NUMB	Breast cancer	Increases stemness.	(Yang et al., 2021b)
miR-140-5p	PD-L1	Hepatocellular carcinoma	Attenuates the stemness induced by sorafenib.	(Zhao et al., 2021a)
miR-205	VEGF	Ovarian cancer	Suppresses apoptosis.	(Wang et al., 2019b)
miR-15a	SALL4	Hepatocellular carcinoma	Promotes apoptosis.	(Ma et al., 2021)
miR-338-3p	CHL1	Non-small-cell lung cancer	Increases apoptosis.	(Tian et al., 2021)
miR-21-5p	CDK6	Ovarian cancer	Suppresses apoptosis.	(Cao et al., 2021)
miR-34a	IL-6R, STAT3, PD-L1, and VEGF-A	Colorectal cancer	Promotes apoptosis.	(Hosseini et al., 2021)
miR-101-3p and miR-423-5p	FOXP4 and EZH2	Medulloblastoma	Increases apoptosis.	(Xue et al., 2022)
miR-107	HMGA2	Gastric cancer	Enhances the sensitivity of resistant cancer cells to chemotherapeutic agents.	(Jiang et al., 2021)
miR-148b-3p	PTEN	Bladder cancer	Enhances chemosensitivity.	(Shan et al., 2021)
miR-205	E2F1	Breast cancer	Promotes tamoxifen resistance.	(Zhao et al., 2021b)
miR-208b	PDCD4	Colorectal cancer	Induces oxaliplatin resistance.	(Ning et al., 2021)
miR-106a-5p	ARNT2	Nasopharyngeal carcinoma	Contributes to cisplatin resistance.	(Li et al., 2021)
miRNA-25-3p	FBXW7	Glioblastoma	Promotes temozolomide resistance.	(Wang et al., 2021b)
miR-1298-5p	SETD7 and MSH2	Glioma	Promotes the immunosuppressive effects of MDSCs.	(Qi et al., 2022)
miR-135b-5p	SP1	Gastric cancer	Impairs the function of Vγ9Vδ2 T cells.	(Li et al., 2022b)
miR-1468-5p	HMBOX1	Cervical cancer	Allows cancer cells to escape anti-cancer immunity.	(Zhou et al., 2021)
miR-107	DICER1 and PTEN	Gastric cancer	Induces the expansion and activation of MDSCs	(Ren et al., 2019)

they can affect how cancer cells develop and how well they respond to treatment. Exosomes may contribute to radioresistance in addition to medication resistance. Exosomes can also reduce T cell cytotoxicity, promote immunological evasion, and cause immune cell fatigue. Exosomes accelerate the development of cancer by inducing persistent inflammation. They can concentrate on these elements when novel therapies are brought into clinics to treat cancer patients.

Funding

None.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgement

This study was supported by the Medical Laboratories Techniques Department, Al-Mustaqbal University College, Babylon, Hilla, Iraq.

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