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EDITED BY

Abdullah Saeed,
City of Hope National Medical Center,
United States

REVIEWED BY

Sheefa Mirza,
University of Witwatersrand, South Africa
Ying Liang,
Air Force Medical University, China

*CORRESPONDENCE

Sivakumar Arumugam

✉ siva_kumar.a@vit.ac.in

Janaki Ramaiah Mekala

✉ janakiramaiah.m@vit.ac.in

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Targeting cancer via macrophage-derived exosomal miRNAs: implications for tumor progression and resistance

Prasanna Srinivasan Ramalingam¹, Muhammad Afzal², M. Arockia Babu³, Rekha M. M.⁴, Samir Sahoo⁵, Surya Nath Pandey⁶, Haider Ali⁷, Md Sadique Hussain⁸, Gaurav Gupta^{9,10}, Janaki Ramaiah Mekala^{11*} and Sivakumar Arumugam^{1*}

¹Protein Engineering Lab, School of Biosciences and Technology, Vellore Institute of Technology, Vellore, Tamil Nadu, India, ²Department of Pharmaceutical Sciences, Pharmacy Program, Batterjee Medical College, Jeddah, Saudi Arabia, ³Institute of Pharmaceutical Research, GLA University, Mathura, Uttar Pradesh, India, ⁴Department of Chemistry and Biochemistry, School of Sciences, JAIN (Deemed to Be University), Bengaluru, Karnataka, India, ⁵Department of General Medicine, IMS & SUM Hospital, Siksha 'O' Anusandhan (Deemed to be University), Bhubaneswar, Odisha, India, ⁶Department of Pharmacology, Teerthanker Mahaveer College of Pharmacy, Teerthanker Mahaveer University, Moradabad, Uttar Pradesh, India, ⁷Department of Pharmacology, Kyrgyz State Medical College, Bishkek, Kyrgyzstan, ⁸Uttaranchal Institute of Pharmaceutical Sciences, Uttaranchal University, Dehradun, Uttarakhand, India, ⁹Centre for Research Impact and Outcome-Chitkara College of Pharmacy, Chitkara University, Rajpura, Punjab, India, ¹⁰Centre of Medical and Bio-allied Health Sciences Research, Ajman University, Ajman, United Arab Emirates, ¹¹Department of Integrative Biology, School of Biosciences and Technology, Vellore Institute of Technology, Vellore, Tamil Nadu, India

Recent studies on macrophages showed their contribution to tumorigenesis, progression, metastasis, and chemoresistance by influencing the local tumor microenvironment and cancer cells. Exosomes form a subset of extracellular vesicles and have played a major role in the interaction between cancer cells and macrophages. This review intends to discuss the existing literature on employing macrophage-derived exosomes as a vehicle for microRNA (miRNA) delivery in oncological applications. It will evaluate the molecular principles of this therapeutic approach and its capacity to enhance cancer therapy by elucidating problems like drug and radio-resistance. This review uniquely emphasizes the diagnostic and therapeutic potential of macrophage-derived exosomal miRNAs, summarizing current understandings into their molecular processes, tumor specificity, and strategies to overcome therapeutic resistance. This review synthesizes recent studies and evaluates how macrophage-derived exosomes and their miRNAs contribute to cancers. These vesicles are multipurpose tools that regulate tumor behavior, considering they can regulate it through post-transcriptional regulation and protein phosphorylation. Such exosomes that are engineered can potentially introduce a novel dimension because they have the capability of delivering targeted oncogenic or tumor-

suppressive miRNAs to overcome limitations of current cancer therapeutics, particularly drug and radioresistance. Engineered macrophage-derived exosomes may thus have the potential as a novel approach for cancer treatment and overcoming therapeutic resistance.

KEYWORDS

cancer biomarkers, exosomal miRNAs, macrophage-derived exosomes, therapeutic resistance, tumor-associated macrophages, tumor microenvironment

1 Introduction

Exosomes are extracellular vesicles (EVs), typically 30–150 nm in diameter, secreted by various cells, such as cancer and immune cells or stromal cells (1). Proteins, nucleic acids, and lipids carried by these vesicles are biologically active and mediate intercellular communication (2). Exosomes have been in the limelight in the field of oncology and are already regarded as significant contributors to the tumor microenvironment (TME) (3). They participate in numerous processes essential to tumorigenesis, e.g., tumor growth, metastasis, immune evasion, and the development of drug resistance (4). The fact that exosomes can induce plasticity in the recipient cells, mostly through inciting malignant transformation, makes them an indispensable to cancer development and a target for therapeutic intervention (5, 6). Exosomes form as intraluminal vesicles (ILVs) in multivesicular bodies (MVBs) and are released by fusion with the plasma membrane; their proteins, lipids, and nucleic acid cargo can reprogram recipient cells within the TME (7). In cancers, tumor-associated macrophages (TAMs) tend to be biased towards immunoregulatory M2-like phenotypes, with the M1-like macrophages being pro-inflammatory. Meanwhile, macrophage-derived exosomes (MDEs) are exosomes that are released by macrophages; their microRNA (miRNA) cargo (MDE-miRNAs) can be suggestive of macrophage polarization and local stimuli and reorganize tumor growth, metastasis, immune evasion, and therapeutic resistance (8, 9). MDEs may play an important role in cancer biology (10). The TAMs are primarily polarized to a pro-tumorigenic phenotype (11). These TAMs will be involved in circuits maintaining tumor growth, angiogenesis, or invasion/metastasis, which may reprogram cancer behavior (12). By transmitting such a load, MDEs stimulate tumor cell survival and growth and invasion, and the development of an immunosuppressed microenvironment hostile to immune editing by tumor cells (13, 14).

Recent advancements in studies have navigated this avenue of MDE therapeutics, particularly with regard to the delivery of miRNA to cancer cells. Selective treatment based on the affinity of MDEs to areas of tumors creates an appealing treatment strategy (15). Targeted delivery of therapeutic miRNAs resulting in gene modulation via MDEs has the potential to prevent the advancement of cancer and overcome the limitations present in conventional nanocarriers (16). In addition, individual variability in MDEs across cancers is the rationale

for personalized medicine approaches (17). MiRNA content personalization in MDEs with the help of the tumor environment signature can lead to amelioration and personalized intervention (18). Developments in our understanding of the complexity of MDEs in cancer hold great possibilities to be further exploited as potential markers and as therapeutic vehicles in this context to allow the creation of specific new treatment paradigms (19). Even though exosome biogenesis is common across cell types, it is the cell of origin that leaves a mark on cargo and cellular functions (20). Relative to tumor-derived exosomes (TDEs) that tend to exacerbate oncogenic messaging in cancer cells, MDEs predominantly inform the TME and remodel cancer cells, stromal cells, and immunity by miRNAs associated with the macrophage state. They also exhibit tropism for hypoxic tumor subregions, and MDEs carry immunomodulatory signals that are less noticeable in alternative stromal exosomes. Although there is growing evidence on the diverse functions, there is inadequate systematic knowledge on how macrophage-derived exosomal miRNAs determine tumor biology and respond to therapy. The review is a summary of contemporary information on their mechanistic contributions, clinical associations with multiple large-scale cancer types, and obstacles to utilizing them in translation research. Given their dual potential role in tumor promotion and suppression, these exosomes represent a promising yet underexplored therapeutic avenue. The primary focus in this review is MDEs; other exosomes released by tumor cells or other stromal cells are only mentioned in the form of contrast where necessary. Understanding their molecular mechanisms and translational potential could unlock innovative strategies to overcome drug and radioresistance, paving the way for more precise and effective cancer treatments. In this review, we have explored the potential of Macrophage-derived exosomal miRNAs in tumor progression and resistance.

2 Biogenesis of macrophage-derived exosomes

2.1 Mechanisms of exosome formation

The biogenesis of exosomes initiates with the internal budding of the cellular plasma membrane, leading to small vesicle-like

structures called early endosomes; this is followed by a highly complex process known as MVBs formation (21). Subsequent invagination of these early endosomes leads to the formation of ILVs within MVBs (22). One of these steps is the formation of ILVs, which are important precursor vesicles containing bioactive cargo that will ultimately be delivered to recipient cells in exosomes (23). The membrane of these endosomes is then remodeled and organized into discrete domains that are enriched in particular proteins, lipids, or nucleic acids (24). This sorting process is mostly selective, by which only specific molecules are included in exosomes (25). After MVBs reach full maturation, they either fuse with lysosomes for degradation or fuse with the plasma membrane and release ILVs as exosomes into the extracellular space (26). The choice between these fates is controlled by several signaling pathways and molecule interactions that are the subject matter of ongoing research (27). At the heart of this endosomal maturation process are Ras-associated binding (Rab) GTPases that direct MVBs to fuse with the cell surface through SNARE protein-dependent final fusion (28). Exosomes are released into the extracellular space to act as a mode of intercellular communication, particularly within the TME, thus influencing cancer progression (Figure 1) (29). The polarization state (M1 vs. M2/TAM) of macrophages in particular alters miRNA abundance and loading in exosomes through established sorting pathways to remodel the exosomal repertoire.

Polarization leaves different miRNA signatures on the MDEs with functional implications in the tumor. M1-polarized macrophages specifically pack miR-155-5p into exosomes (greater in M1 than in M0/M2), and M1-exosomal miRNA can have anti-

tumor effects in several models. Conversely, the reports of M2/TAM exosomes being repeatedly highly enriched with oncogenic miRNAs that engage cancer cells and trigger activated pro-survival signatures and invasion, and chemoresistance are recurrently mentioned (30). Mechanistically, such polarization-specific differences in cargo fold into general pathways of exosome sorting, hnRNP A2B1 attachment to EXO motifs (31), YBX1-selection (e.g., of miR-223) (32), relative enrichment of 3'-uridylylated isoforms in exosomes (33), and ceramide/neutral sphingomyelinase 2 (nSMase2)-mediated miRNA export (34) to provide a macrophage-specific basis to how M1 versus M2 states bias the exosomes-mediated miRNA positing.

2.2 Role of ESCRT machinery and other molecular players

The endosomal sorting complexes required for transport (ESCRT) machinery is an ATP-dependent mechanism that functions in the packaging of cargo into intraluminal vesicles (ILVs) within multivesicular bodies (MVBs), a critical step during exosome biogenesis (35). The ESCRT machine consists of four large complexes that include ESCRT-0, I, II, and III. Various complexes perform different roles in the process of exosome production (36). The major role of ESCRT-0 is to identify and enclose the cargo tagged with ubiquitin at the endosome membrane. During the formation of the MVBs, ILVs are generated by the process catalyzed by ESCRT-I and ESCRT-II. Meanwhile, ESCRT-III

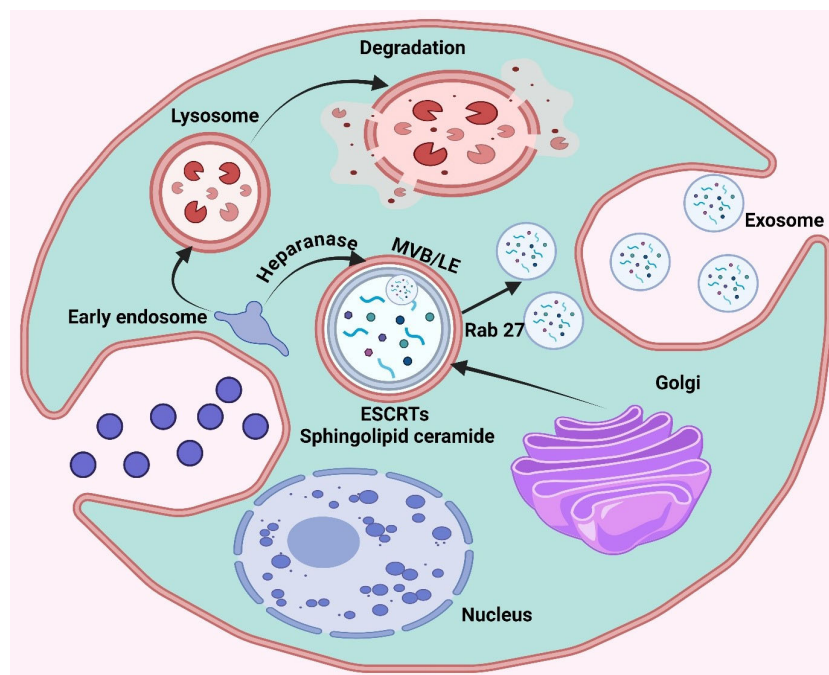


FIGURE 1

The graphic illustrates the cellular process of exosome production. This diagram depicts the process of early endosome creation leading to the production of multivesicular bodies (MVB/LE) and the eventual release of exosomes, as well as the routes involved in lysosomal degradation. Important compounds include ESCRT, Rab27, and sphingolipid ceramide.

performs a last separation by breaking membranes to release nascent ILVs inside the lumen of MVB (37).

A wide variety of accessory proteins has also been shown to be involved in exosome biogenesis in addition to the ESCRT complexes (38). Alix and TSG101 are significant regulators that get involved with the ESCRT apparatus in orchestrating proper cargo sorting/packaging. Alix plays a critical role in the process of budding, and TSG101 associates with the ubiquitinated protein to mark them in the immature exosomes (39). Along with this, other molecular elements such as Rab GTPases are also necessary to release exosomes in the plasma membrane through transport and docking of MVBs (40). Two of the Rab family members, namely Rab27a and Rab27b have been demonstrated as being critical in the localization of MVBs near the plasma membrane through exosome release. Newer studies have also indicated the orchestration of the lipid nanodomains (also called as room rafts) in the exosome biogenesis (41). These membrane lipid-rich areas serve as protein complex scaffolds that participate in exosome formation (42). Consequently, the biophysical nature of such microdomains is significantly modulated by cholesterol, sphingomyelin, and ceramide, and hence various abilities to convert them to exosomes (43).

2.3 Influence of external stimuli

The generation and secretion of MDE are induced by external factors such as hypoxia, inflammation, or oxidative stress. EV content changes in the hypoxic, acidic, and low glucose TME, which leads to alterations in their function (44). Hypoxia is a hallmark of solid tumors known to promote the secretion of exosomes from cancer cells and TAMs (45). Exosomal cargo is likewise altered under hypoxic conditions that tend to enrich for pro-angiogenic factors such as miRNA and vascular endothelial growth factor (VEGF), enhancing metastasis. These observations suggest that not only does hypoxia produce exosomes, but it also modifies their cargo to the advantage of tumor progression (46). In line with its inflammatory status, which is well characterized in cancer, exosome biogenesis was also altered. The released exosomes contain additional protein and RNA cargo when macrophages are exposed to inflammatory cytokines such as TNF- α or IL-6 (47, 48). Studies have demonstrated that exosomes secreted from inflamed cells can deliver immunosuppressive molecules to dampen the activation of cytotoxic T cells and facilitate immune evasion (49). On the other hand, cellular stress, such as that induced by oxidative stress and nutrient deprivation or provoked by treatment with chemotherapeutic agents, may result in increased exosome secretion (50, 51). This stress-induced exosomal secretion is believed to represent a cytoprotective process that removes deleterious proteins and RNAs from cells, as well as modulates the TME, which further influences cancer cell proliferation/survival in response to treatment (52).

3 Functions of MDEs in cancer

The MDEs significantly contribute to tumor biology through intercellular communication in the TME. These vesicles convey

regulatory miRNAs, proteins, and lipids that significantly affect cancer cells' surrounding stroma. MDEs can lead to tumor progression, angiogenesis, invasion, and immune suppression and therapy resistance depending on their molecular cargo (53). The subsections below provide an overview of the key MDE-regulated processes in cancer progression.

3.1 MDEs promote tumor proliferation

One of the major functionalities that MDEs carry out in case of cancer is to create a suitable condition for tumor growth and proliferation (54). Oncogenic dysregulation of MDEs often involves oncogenic miRNAs and proteins to instigate signaling pathways in human cancer cells, e.g., PI3K/AKT or Wnt/ β -catenin pathway that brings about increased cell proliferation/survival (55). MiR-501-3p in M2-exosomes favors tumor progression by triggering the transforming growth factor- β (TGF- β) cascade and suppressing the tumor suppressor gene TGFBR3 (56). In human epithelial ovarian cancer (EOC), exosomal miR-221-3p derived from M2 macrophages promotes cancer growth by reducing the cyclin-dependent kinase inhibitor 1B (CDKN1B) (57). A separate investigation indicates that exosomal miR-29a-3p and miR-21-5p derived from M2 macrophages increase the proportion of T regulatory cells (Tregs) to T helper cell 17 (Th17), thereby contributing to a tumor immune inhibitory TME and facilitating the development of cancer and metastasis (58). The data indicate that macrophage-derived exosomal miRNAs target not only cancerous cells directly but also the immune systems, thereby influencing cancer cells indirectly.

3.2 MDEs promote metastasis

Moreover, MDEs modulate the TME by modifying stromal cell behavior, favoring angiogenesis, and establishing a permissive niche for many phases of tumorigenesis. MDEs are also involved in promoting the metastatic ability of cancer cells (59, 60). Through the transmission of pro-metastatic molecules, MDEs can reshape extracellular matrices to promote cancer cell invasiveness and assist in developing pre-metastatic niches at target organs (61). M2-Exos carry lncRNA AFAP1-AS1, downregulating miR-26a and upregulating activating transcription factor 2 (ATF2), hence facilitating esophageal cancer (EC) penetration and metastasis. Engaging M2 macrophages and the lncRNA AFAP1AS1/miR-26a/ATF2 pathway is a promising treatment option for EC (62). Lan et al. observed that M2-Exos regulate Brahma-related gene 1 (BRG1) by delivering miR-21 and miR-155-5p, leading to the downregulation of BRG1 and promoting colorectal cancer (CRC) metastasis (63).

3.3 MDEs confer drug resistance

Furthermore, MDEs are also involved in drug resistance to cancer. They can take up and transmit miRNAs, as well as other

molecules that regulate the expression of drug-resistance genes in cancer cells, which helps reduce both chemotherapeutic response and response to targeted therapies (64, 65). Such exosome-mediated communication develops a multidrug-resistant and aggressive tumor phenotype. Recent data indicate that MDEs-derived miRNAs exert an inhibitory effect on cancer. MDEs, rich in miR-7, are internalized by EOC cells following treatment with tumor necrosis factor-like weak inducer of apoptosis (TWEAK). This internalization inhibits cell invasion by targeting the EGFR-mediated AKT/ERK system (66). MDEs miR-let-7a-5p can be transferred to lung cancer cells, resulting in the inhibition of cell growth, migration, and invasion through the downregulation of Bcl2-like 1 (BCL2L1) expression (67).

3.4 MDEs regulate immune responses

MDEs partake in the immune regulation within the TME (68). Consequently, these cells can modulate anti-tumor immune responses by affecting the function of different types of innate and adaptive immunity effector cells, leading to immunostimulants and cancer progression (69).

4 miRNA loading and cargo selection in MDEs

MiRNA loading and cargo selection in MDEs is a tightly regulated transcriptional program that dictates response to various stimuli, including cancer (70). Besides, the selective incorporation of specific miRNAs and other bioactive molecules into MDEs is not random, as specific cellular mechanisms mediate this process to provide directed signaling to recipient cells. MiRNA incorporation into MDEs occurs during the biogenesis of these vesicles in parent mesenchymal stromal/stem cells (MSCs) (71, 72). Many important proteins and pathways participate in modulating the selective packaging of miRNAs (73, 74). Key players for recognizing and mediating the loading of selected miRNAs into MDEs are those represented by RNA-binding proteins (RBPs), such as Argonaute 2 (Ago2), heterogeneous nuclear ribonucleoproteins, and endosomal sorting complexes required for transport (75, 76). Exosome-targeting motifs (EXO-motifs; GGAG/UGGA-like motifs) and U/CA-rich elements are preferentially bound by hnRNP family proteins, in macrophages, enhancing their export in budding intraluminal vesicles. The miRNAs that interact with Ago2 are selectively targeted to exosomes by a combination of their stable seed imaginary pairing potential and their preference for 5'-nucleotides to interact with Ago2. Additional sequence-independent sorting bias modulates RBP affinity/retention, versus export decisions are affected by secondary structure and 3'-end modifications. A combination of these features can be used to operationalize the selective, non-random packaging of miRNAs into macrophage-derived exosomes. In practice, these RBPs read the above EXO-motifs, U/CA-rich elements, 3'-end marks, and exposed hairpins to triage individual miRNAs for vesicular export,

committing them as cargo precursors during ILV budding within maturing MVBs (77). The miRNAs are then loaded into the intraluminal vesicles, which, after the bulbs are fused to the plasma membrane, lead to the release of MDEs out of the cell. The miRNA content of MDEs may reflect the physiological status of MSCs and even stimuli from external surroundings (78, 79). Under hypoxic conditions or in response to inflammatory signals, MSCs may selectively furnish MDEs with different miRNA cargos (i.e., pro-angiogenic miRs for TME redirecting recipient cancer cells and immunomodulatory miRs preventing anti-tumoral immune cell activation) (80). Hypoxia, which is a characteristic of solid tumors, enhances exosome release by TAMs and cargo composition, in part by altering the expression and post-translational status of RBPs, favoring certain motifs and diminishing others (81). Cellular stress and inflammatory cytokines also reprogram exosomes' biogenesis and cargo selection, enriching pro-angiogenic or immunomodulatory miRNAs and reconfiguring the TME (82). Such context-dependent modifications justify the reason why exosomes of hypoxia-related, macrophage-produced exosomes often carry pro-metastatic/therapy-resistance miRNAs, which are evident throughout Section 5.

In addition to miRNAs, MDEs also selectively incorporate other molecular cargo, such as proteins, lipids, and lncRNA, under specific cellular contexts to mediate a targeted biological effect (83–85). The cargo sorting is indispensable to the function of MDEs in regulating the TME, promoting metastasis, and inducing drug resistance (86). The interaction between miRNAs and other cargo components in MDEs may enhance their potency on recipient cells synergistically (87). The miRNA cargo of MDEs in cancer can downregulate tumor suppressor genes or upregulate oncogenes in recipient cells, leading to the promotion of tumorigenesis and metastasis. Additionally, MDEs could be artificially designed to carry tumor-suppressive miRNAs and serve as a therapeutic strategy (88–90). Elucidating these processes in MDEs will be critical for the future design of targeted therapies that either suppress the pathological functions of MDEs or use them to deliver therapeutic molecules in cancer and potentially other diseases (91).

5 Applications of miRNA-loaded macrophage-derived exosomes as delivery vehicles

For a cross-comparison of key MDE-miRNAs, their validated targets, and net functional outcome across cancers, refer to [Table 1](#).

5.1 Lung cancer

Lung cancer, the most lethal of all cancers worldwide, arises principally in cells that line the airways. This is generally divided into non-small cell lung cancer (NSCLC), which represents around 85% of cases, and small cell lung cancer, which is more aggressive

(98). This disease is associated with risk factors like smoking, carcinogen exposure, and genetic predisposition. The early stage of lung cancer is often asymptomatic; thus, most patients present with advanced disease at diagnosis, and they usually have a poor prognosis (99, 100). Lung cancer is the leading cause of cancer deaths, with more than 2 million new cases reported every year worldwide, especially in developing countries where smoking rates are high. It occurs much more often among men, although it is becoming an increasingly common problem with women (101). Currently, despite increasingly effective surgical and chemotherapeutic treatments, the five-year survival rate is only around 20%, mainly due to the late detection of disease with its aggressive nature (102, 103). There is a growing realization that miRNAs are key players in gene expression closely associated with lung tumor development, progression to advanced disease, and therapeutic resistance (104, 105). All these miRNAs can work as oncomiRs or tumor suppressor genes, influencing key regulators implicated in cell proliferation, apoptosis, and metastasis (106, 107). Considering the ability of miRNAs to serve as both blood-based markers for early detection and prognosis, in addition to being therapeutic targets themselves, they represent a novel target group in personalized treatment strategies for lung cancer (108). For instance, let-7a-5p downregulates the oncogene BCL2L1 by thereby targeting it for gene silencing through association with a specific mRNA encoding protein activity that affects multiple signaling transcripts and inhibiting cell proliferation and migration/invasive phenotype in lung cancer (109). The miRNA activates the PI3K γ signaling pathway and induces autophagy and apoptosis in human lung cancer cells (110). Duan et al. utilized let-7a-5p as exosome cargo because high levels of this miRNA in macrophages hinder lung cancer, and the cells also treated A549 NSCLC with BCL2L1 are targets. Surprisingly, let-7a-5p upregulation induced autophagy and cell death in lung cancer cells without triggering apoptosis or pyroptosis (Figure 2) (111).

The biological role of TNF- α in lung cancer is paradoxical, being capable of both averting tumor proliferation and also

facilitating it (112, 113). On the one hand, this cytokine can mediate inflammation and promote tumor growth through activating transduction pathways that enhance cell survival processes like nuclear factor- κ B (NF- κ B). It acts alone or together with other agents under various conditions, selectively kills cancer cells by apoptosis cascade clearance mediated through ligating its receptor pathway (114, 115). Jiao et al. identified that TNF- α -stimulated exosomes of PMNs were implicated in sepsis-related ALI, promoting M1 macrophage activation and pyroptosis via the NF- κ B signal pathway. Inhibition of this pathway is regulated by exosomal miR-30d-5p directly targeting SOCS1/SIRT1 in macrophages. Knocking down miR-30d-5p decreased the pyroptosis, macrophage activation, and lung injury in sepsis-related acute lung injury (ALI) rats by inhibiting PMN-M interaction via a novel mechanism; these results suggest new potential therapeutic targets for treating sepsis (116).

Moreover, the use of certain microRNAs as diagnostic biomarkers led to progress in the early detection of lung cancer (117). Cazzoli et al. discovered microRNAs able to distinguish lung adenocarcinomas from benign lung conditions with sensitivities and specificities exceeding 90 percent. Their screening test was 97.5% sensitive and 72.0% specific, whereas, for lung adenocarcinoma versus granulomas, their diagnostic assay had a sensitivity of 96.0%, with a specificity of only 60%. This implies a promise of using circulating exosomal miRNAs as early diagnostic markers for lung cancer (118). In addition, Munagala et al. showed that miR-21 and miR-155 exhibited higher levels of the two sequences in serum exosomes from recurrent lung tumors compared to primary ones. These miRNAs are proposed to be potential biomarkers for non-invasive diagnosis of recurrent lung cancer, as their expression patterns in exosomes overlap with those of pathological tissues from primary and metastatic lung tumors. Consequently, miRNAs serve as potential markers of disease progression and relapse monitoring (119). Exosomal miRNAs including let-7a-5p, miR-21, and miR-155 that are released by macrophages influence both the proliferation of tumors and

TABLE 1 Comparative summary of macrophage-derived exosomal (MDE) miRNAs across cancers.

Cancer type	Key MDE-miRNA(s)	Validated direct target(s) in recipient cell	Functional outcome	References
Ovarian (EOC)	miR-223	PTEN	Tumor-promoting (chemoresistance via PI3K/AKT activation).	(92)
Gastric	miR-21	PTEN	Tumor-promoting (cisplatin resistance; PI3K/AKT).	(93)
PDAC	miR-365	CDA induction/nucleotide pool remodeling (gemcitabine inactivation)	Tumor-promoting (drug resistance).	(94)
PDAC	miR-501-3p	TGFBR3	Tumor-promoting (TGF- β activation; invasion/metastasis).	(56)
NSCLC	miR-155; miR-196a-5p	RASSF4	Tumor-promoting (EMT, migration, metastasis).	(95)
CRC	miR-155-5p	ZC3H12B ($\uparrow$ IL-6 stability)	Tumor-promoting (immune escape/tumor formation).	(96)
Melanoma	miR-29c-3p (from M1 macrophages)	ENPP2	Suppressive (reduced aggressiveness).	(97)

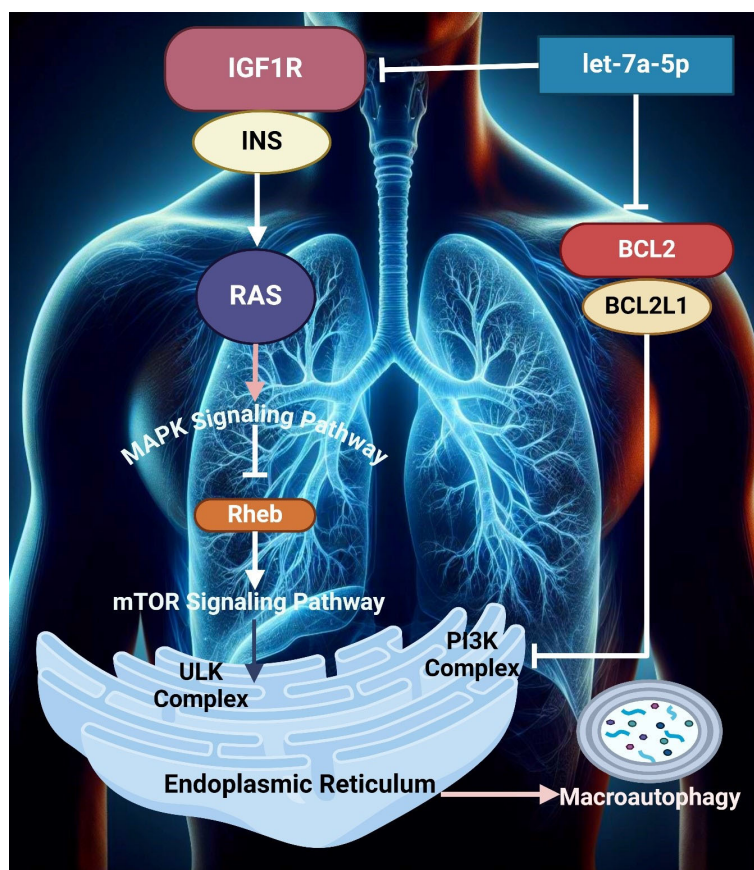


FIGURE 2

The image illustrates key signaling pathways involved in lung cellular processes, highlighting the MAPK and mTOR pathways. It depicts the interaction between IGF1R, INS, and RAS and the downstream effects on autophagy through the endoplasmic reticulum, mediated by Rheb and PI3K complexes.

development of drug-resistance as well as function as non-invasive diagnostic and predictive biomarkers that can be detected in serum exosomes (120, 121), which has a practical value in screening and monitoring drug-resistance lung cancer in early diagnosis and the chosen therapeutic response and treatment.

5.2 Breast cancer

Breast cancer is the most frequently diagnosed of all cancers among women, with the highest incidence rates in North America and Europe; it originates in ducts (ductal carcinoma) or lobules (lobular carcinoma) (122). With the capacity to metastasize, this cancer can spread all over, and hence its early detection matters (112, 113, 123). The prognosis has substantially improved with the advent of screening methods such as mammography, which allows early detection. There are many treatments for breast cancer, which vary depending on the stage of the disease and its characteristics (124–126). Although the disease is much more common in women over 50, even men can have breast cancer. Age, genetic mutations (e.g., BRCA1/2), family history, reproductive history, and lifestyle factors. Although advancements in detection and treatment have improved survival rates, disparities persist, influenced by geographic, socioeconomic, and racial factors (127).

MiRNAs are involved in the post-transcriptional regulation of gene expression and play a fundamental role in breast cancer by controlling genes related to growth, metastasis, or resistance to therapy. These miRNAs exert oncogenic or tumor suppressor roles modulating key signaling pathways that lead to cancer development (128–130). Due to their potential as biomarkers for diagnosis and prognosis or even therapeutic targets, miRNAs are of great interest in breast cancer research workflow development. In breast cancer, bone marrow stromal macrophages exert a dual effect on both cancer cell dormancy and chemoresistance (131). The M2 macrophages are mainly associated with the induction of dormancy and chemoresistance to cancer cells. The M1 macrophages, however, counteract the dormancy, reactivating the cancer cells and making them more susceptible to chemotherapy (132). This balance is essential in the determination of both dormancy and susceptibility to the treatment of breast cancer in the bone marrow (133). Walker et al. revealed that bone marrow stromal macrophages induced breast cancer cell dormancy, with M2 cells enhancing quiescence and resistance to carboplatin via a gap junctional communication. However, the process was reversed by the M1 cells, which activated NF- κ B, increased cellular sensitivity to carboplatin, and improved the survival of the hosts. Driving the modulation of the macrophage phenotype could be the

preferred treatment option to control breast cancer dormancy. This will hinder cancer cells from spreading to other parts of the body (134).

Exosomes, as one of the types of microvesicles, are of paramount importance in breast cancer, as they help cells communicate with each other (135). Cells are capable of transferring oncogenic molecules, including several forms of miRNA, proteins, and lipids responsible for the cells' promotion of tumor growth, invasion, and metastasis (136). Exosomes are of essential importance due to their role in forming the TME (137). According to the study by Yang et al., IL-4-activated macrophages enhance the invasion of breast cancer cells by transferring miR-223. The latter, in turn, raises the invasiveness of cancer cells through the Mef2c- β -catenin pathway. Inhibition of miR-223 in macrophages decreases the suppressive effect of these cells on the invasiveness of breast cancer cells in co-culture, demonstrating the pivotal role of the exosomal transfer of miRNAs in the interaction of macrophages with breast cancer cells that promotes metastasis (138).

One of the leading accelerators of breast cancer development is TAMs. They provide favorable conditions for tumors by enhancing growth, invasion, and metastasis and promoting angiogenesis, immune escape, and tissue remodeling in the TME (139, 140). In most cases, TAMs are oriented toward the M2 type, as it is closely related to the poor prognosis of breast cancer patients (141). The study of Li et al. shows that miR-146a and miR-222 are downregulated, which contributes to tumor progression. Specifically, miR-146a promotes M2 macrophage polarization, which accelerates tumor progression. Secondly, miR-222 inhibits TAM chemotaxis by targeting C-X-C chemokine receptor type 4 (CXCR4) and C-X-C motif chemokine ligand 12 (CXCL12), which ultimately suppresses tumor growth *in vivo*. Thus, miRNAs are a significant factor in regulating TAM functioning and the rate of breast cancer progression (142). MDEs' miRNAs such as miR-223 and miR-146a affect metastasis and macrophage polarization and hence connect macrophage polarization with tumor aggressiveness and immune evasion (120, 143). Their constancy is contributed by their exosomal state that allows food to nurture them as floating biomarkers and possible agents to reverse this chemoresistance within breast cancer.

5.3 Ovarian cancer

Ovarian cancer is a malignancy that starts in the ovaries and often goes undetected until it has spread within the pelvis and abdomen. Therefore, ovarian cancer is the most malignant of gynecologic cancers due to late diagnosis (144, 145). The disease reportedly has several subtypes, including EOC, which is the most common. Generally, however, ovarian cancer is usually manifested by non-specific symptoms such as bloating, pelvic pain, and changes in bowel habits, which makes its detection at early stages quite challenging (146). Moreover, the disease is the eighth most common type of cancer among women worldwide, in addition to being the greatest cause of death from all gynecologic malignancies (147, 148). Ovarian cancer is more commonly reported in Europe

and North America than in other parts of the world (149). The disease is mainly encountered among postmenopausal women, with a median age at diagnosis standing at 63 years. Despite the rapid increase in the number of ovarian cancer treatment options, the overall 5-year survival rate remains less than 50% due to its tendency to be diagnosed in late stages (150). In particular, risk factors are common and include age, family history of ovarian cancer, family history of breast cancer, a personal history of breast or ovarian cancer, BRCA1 or BRCA2 mutation, never having given birth, and estrogen hormone therapy (151).

Ovarian cancer depends on oncogenic or tumor suppressor miRNAs that control gene expression involved in tumor development, invasion, and resistance to chemotherapy. Some miRNAs have been strongly linked to poor clinical outcomes in ovarian cancer and have been proposed as early diagnostic or therapeutic targets (152, 153). Li et al. found that exosomal miR-221-3p originating in TAMs drives late EOC progression via CDKN1B inhibition and is selectively enriched in M2 exosomes. miR-221-3p is highly enriched in both the cytoplasm and nucleus of M2 exosomes and appears to stimulate the G1/S phase transmission of EOC cells. The results of this study identify exosomal miR-221-3p as a potential diagnostic serum EOC biomarker and a novel M2-derived target for EOC therapy (57).

GATA3 is a transcription factor involved in breast cancer. However, its role in ovarian cancer cells is also emerging as an important finding. These vital factors are often found in cells, which contribute to the progression of the tumor (154). Tumor cells become aggressive by modulating the TME. GATA3 can also activate other associated pathways (155) in a study conducted by El-Arabey et al. GATA3 is demonstrated to be released from TAMs in an exosomal form. This also activates macrophage polarization and its interaction with High-grade serous carcinoma (HGSOC) cells. It facilitates tumor growth and epithelial-mesenchymal transformation. Major tumor-stimulating effects are reduced by the use of siRNA in the GATA3-targeted TAMs. Therefore, GATA3 acts as an important marker for prognosis and a better therapeutic technique for HGSOC (Figure 3) (156). The interaction between regulatory T cells and Th17 cells within the TME serves to define the type and the intensity of immune response-resistant EOC, which, as a rule, defines the clinical course and treatment results (157, 158). Tregs play a rather valuable role in boosting tumors, offering a suppressive effect on anti-tumor immunity. In contrast, Th17 cells accumulate in tumors in response to the immune response to regulation (159). The study by Zhou et al. investigated the functions of the exosomal miRNAs from TAMs, which are termed miR-29a-3p and miR-21-5p, since they suppress the CD4⁺ T cells in a STAT3 manner. This suppresses the balance of the Treg/Th17 and promotes the progression of EOC in an immunosuppressive atmosphere. This remains clear as targeting the exosomes by the miRNAs may be a novel manner of treating EOC (58).

In ovarian cancer, TWEAK double communicates as it promotes tumor progression and immune perturbation. Namely, TWEAK serves to enhance the proliferation, migration, and resistance of cancer cells by activating the NF- κ B signaling

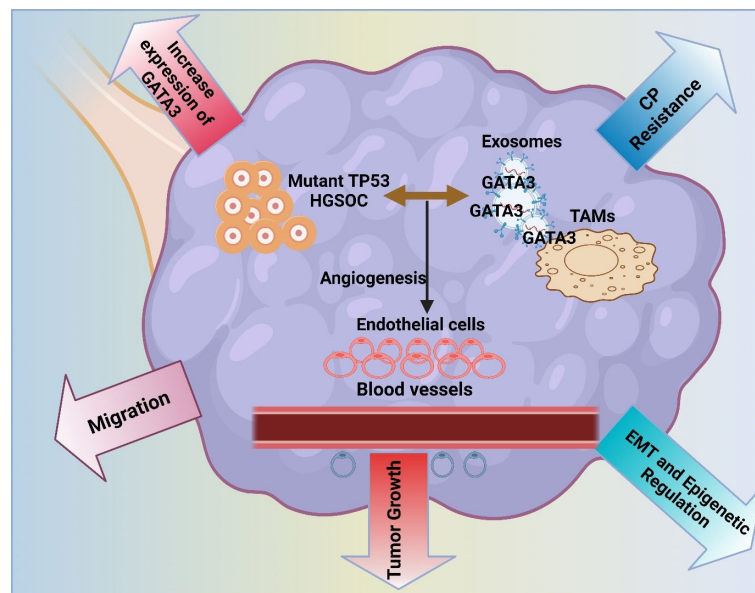


FIGURE 3

The image illustrates the role of mutant TP53 in high-grade serous ovarian cancer (HGSOC), highlighting GATA3 expression's impact on tumor growth, angiogenesis, and migration. It also depicts exosome-mediated communication, contributing to chemoresistance, EMT, and epigenetic regulation in the tumor microenvironment.

pathway (160). Moreover, according to Hu et al., exosomes collected by TWEAK-stimulated macrophages impede the metastasis of ovarian cancer by transmitting miR-7 to EOC cells to reduce passage through the EGFR/AKT/ERK1/2 pathway. Using antagomiR-7 transfection, the levels of miR-7 in the macrophages, exosomes, and EOC cells were reduced, and metastasis was enhanced. Studies in a mixed xenograft rodent model showed that TAMs' exosomal miR-7 prohibits EOC metastasis (66). Besides, Zhu et al. showed that exosomal miR-223 secreted by hypoxic macrophages accelerated the resistance of EOC to chemotherapy by inhibiting the PTEN-PI3K/AKT signaling pathway. Hypoxic exosomes highly expressed miR-223, and they were transferred to EOC to increase its drug resistance. In addition, higher levels of miR-223 contained in the exosomes of patients with EOC were identified in the course of the disease recurrence, which confirms the interaction between macrophages and EOC, which increases the resistance of EOC to chemotherapy (92). M2-macrophage-derived exosomal miR-221-3p, miR-29a-3p, and miR-21-5p are actively amplified to facilitate EOC growth and immune suppression (161). They serve as both clinical agents (correlation in tumor progression prevention) and clinical biomarkers (early detection or monitoring of disease).

5.4 Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the prime variation of primary liver cancer, usually presenting in the background of chronic liver diseases, such as hepatitis B and C, alcoholic liver disease, and non-alcoholic fatty liver disease (NAFLD). Of note, HCC is characterized by its notorious aggressiveness and extremely

poor prognosis (162). Since HCC frequently manifests at an advanced stage, making early detection difficult and curable treatment scarce, this disease is followed by a high rate of death. Regarding the disease frequency, worldwide HCC ranks as the fifth most frequent cancer and the third major cause of cancer death (163). It predominantly affects the male population and has been notably recognized in East Asia and Sub-Saharan African regions, wherein hepatitis B and C infections are common. Nevertheless, in Western countries, this phenomenon is continuously increasing as a result of the burgeoning rates of obesity, diabetes, and NAFLD (164, 165). Notably, the function of miRNAs in HCC is pivotal. It is related to their ability to control gene expression associated with tumor development, progression, and metastasis in either a stimulatory or repressive manner (166).

CD90 is one of the important markers in HCC, and it is Thymus cell antigen 1 (Thy-1), a stem cell antigen that plays an essential role as a marker for cancer stem cells (CSCs). A variety of lines of evidence suggest that CD90+ cells are associated with tumor initiation, progression, and resistance to therapy. CD90+ cells in HCCs exhibit higher self-renewal, invasion, and metastasis properties (167, 168). Wang et al. demonstrated that exosomes from TAMs promote HCC cell proliferation and enhance the relative CSC traits by delivering miR-125a/b. The down-regulation of miR-125a/b in TAM-derived exosomes enhanced CSC traits associated primarily targeting the stem cell marker CD90. These results suggest that miR-125a and miR-125 b play a critical role in the regulation of CSCs in HCC through TAM-derived exosomes (169). Apart from miR-125a/b, miR-142 and miR-223 transfer between the cells substantially contributes to HCC (170). Aucher et al. showed that human macrophages transfer miR-142 and miR-223 to HCC cells via gap junctions. The transfer

inhibits the proliferation of HCC since it regulates the expression of the key proteins, including stathmin-1 and insulin-like growth factor 1 (IGF-1) receptor (IGF1R); thus, a novel defense mechanism of immune cells from tumor proliferation. Multiple mechanisms and processes keep cell proliferation under control, and some of them have been discovered only recently, such as the transfer of small RNA molecules between cells (171).

Alcoholic liver disease is a disorder that is caused by excessive consumption of alcohol. This results in damage to the liver, which could range from fatifying of liver to more severe forms of the disorder, such as alcoholic hepatitis or cirrhosis (172). The chronic consumption of alcohol disrupts the normal functions of the liver cells and is associated with inflammation, which may cause an individual to develop scar tissue on the liver. It increases the risk of liver failure and death and is regarded as a major cause of liver-related incidences of morbidity and mortality in most parts of the world (172). Babuta et al. found that alcohol disrupts autophagy in alcoholic liver disease (ALD) by impairing the functions of autophagosomes and lysosomes. The latter is attributed to the downregulation of Lysosome-Associated Membrane Protein 1 & Protein 2 (LAMP1 and LAMP2). This is a result of miR-155, which targets key oncogenes in the process and causes an increase in the production of exosomes. Notably, the mice that lacked the miR-155 molecule were not affected by the effects, and this proves its role in the disruption of autophagy and the release of exosomes by alcohol in ALD (173). TAM-derived exosomal miR-125a/b, miR-142, and miR-223 control the expression of cancer-stem-cell-associated genes like CD90 that boost tumor recurrence and resistance in HCC (174). Their practical usefulness and their identification in plasma justify their possible use as biomarkers that predict relapse and treat therapeutic nodes in precision-based management of HCC.

5.5 Pancreatic cancer

Pancreatic cancer is a highly aggressive malignancy that originates in the pancreatic tissues and is often detected late, as it is asymptomatic and has rapid progress and a lack of response to any treatments (175). This is the unfinished business of most malignant neoplasms in the pancreas and perhaps one of the most lethal types of cancer. Pancreatic ductal adenocarcinoma (PDAC) is the most common form of pancreatic cancer (176). Risk factors associated with this blockage include cigarette smoking, chronic pancreatitis, being overweight, and having a family history of pancreatic cancer. There are only a several drugs to deal with this diagnosis, which is why the five-year percentile has a very low rate of 5-10% pancreatic cancer (177). Compared to other types of cancer, this one is the twelfth different cancer.

On the other hand, it has a high mortality rate and occupies the seventh place among the deadliest forms of neoplasms. The biggest number of incidence falls in prosperous countries where a large number of men were affected by it (178). People who are obese and have diabetes are also in the high-risk group. One of the critical roles of miRNAs in pancreatic cancer is the involvement in

signaling pathways that control the growth, metastasis, and drug resistance of tumors. This is achieved by miRNAs either as oncogenes or as tumor-suppressive genes (179). Binenbaum et al. discovered that miR-365, which is found in TAMs-derived exosomes in PDAC, impairs gemcitabine activity, which is a drug used in chemotherapy, thus inducing cancer cell resistance to this medicine. The study showed that restoring the latter's sensitivity was possible by blocking miR-365, which provides yet more evidence for the fact that MDEs are among the primary regulators of chemotherapy resistance in PDAC (94).

X-linked inhibitor of apoptosis protein (XIAP) is also a critical factor in pancreatic cancer. It inhibits apoptosis and promotes cell survival. Hence, the XIAP's overexpression in cancer cells guarantees survival despite chemotherapy and other treatments (180). Overexpression of the factor is associated with poor prognosis and the aggressiveness of cancer. Interestingly, XIAP seems to be a practical therapeutic target in pancreatic cancer (181) in the study. Yin et al. show that M2 macrophage-derived exosomes promote pancreatic cancer by transmitting long non-coding RNA SBF2-AS1 that suppresses MiR-122-5p and upregulates XIAP. Suppression of XIAP restrains the tumor from growing, helping treat the disease (182). Similarly, Yin et al., revealed that exosomes in M2 TAMs consist of miR-501-3p to advance PDAC via targeting the suppression gene TGFBR3. This downregulation, in turn, activates the TGF- β signaling pathway that will foster tumor growth and metastasis. Depletion of miR-501-3p in these exosomes acted to suppress tumorigenesis and metastasis, together with their upstream TGF- β signaling pathway, might be viable therapeutic targets for PDAC treatment (56). Macrophage-derived exosomal miR-365 silenced the effect of gemcitabine by interfering with nucleotide metabolism in PDAC, and miR-501-3p and lncRNA SBF2-AS1 changed TGF- β and XIAP to promote chemoresistance (94). These results reveal MDE cargoes as potent drug resistance mediators and promising therapeutic targets tested in *in vivo* xenograft studies.

5.6 Colorectal cancer

CRC is a type of cancer that develops in the colon or rectum. It is often preceded by the growth of benign polyps, which may later become malignant. It is the third most common cancer and the second leading cause of cancer mortality globally (183). The common symptoms experienced are changes in defecation rhythm, bloody stool, and abdominal pain. CRC is monitored by colonoscopy, and when detected, early survival rates are high (184). It is treated with surgery, chemotherapy, and radiation, often in combination. The incidence rates of CRC are third in the most often diagnosed cancers and second in terms of deaths worldwide, with higher rates in the more developed areas, particularly North America, Europe, and Australia (185). There are numerous risk factors, such as age, family history, diet, smoking and alcohol consumption, obesity, and inflammatory bowel diseases. There has been a downward trend in the mortality rates associated with CRC directly linked to the implementation of screening programs,

as the introduction of early detection methods has been decisive (186).

MiRNAs play an essential role in CRC by controlling the expression of genes. These genes are responsible for the growth, metastasis, and response to treatment of the tumor. When miRNAs are not functioning properly, they can become oncogenic or mutated (187). Undeveloped miRNAs have attracted consideration as potential indicators for the first detection of CRC. They are additionally appealing targets for therapeutic intervention and TSR catalysts. There has been an observation that miR-15a and miR-16 are significantly under-expressed in CRC tissues in contrast to the normal mucosa (188). According to the research study of Xiao et al., the low expression of these miRNAs is dependent on the advanced disease degree, poor histological evaluation, and the presence of nodes. The cumulative low level of these two miRNAs can securely guarantee a deficient general and disease-free existence of CRC patients. On this note, the delivery of these miRNAs, which are not well controlled, to the agitated tumors through exosomes may be difficult. The miR-15a and miR-16 are often used as markers for treatment and recovery (189).

The p53 protein is a key player in the mechanism of colon cancer as a tumor suppressor, orchestrating the arrest of the cell cycle, DNA repair, or apoptosis, when necessary, in response to cellular stress or damage to DNA. However, the TP53 gene, which encodes the p53 protein, is mutated in numerous cases of colon cancer, thus losing its function of suppressing tumors (190). In their studies, Cooks et al. found that colon cancer cells with gain-of-function mutp5-3 secrete exosomes containing a high concentration of miR-1246. These exosomes reprogram the TAMs into an anti-inflammatory and cancer-promoting state in CRC through the action of miR-1246. Thus, miR-1246 sustains the immunosuppression, as well as the activity of TGF- β , thus promoting the inflammatory state, as well as the progression of cancer, and poor survival of patients with CRC (191). One of the proteins is ZC3H12B, which is a tumor suppressor in colon cancer, regulating inflammation and cell proliferation (192). The downregulation or loss of ZC3H12B in colon cancer cells results in a more aggressive tumor, increased growth, invasion, and worse prognosis. Such a suppression degrades pro-inflammatory mRNAs, reducing the inflammatory environment that allows cancer to progress (193). Another protein that was identified by Ma et al. is M2 macrophage-derived exosomal miR-155-5p. It fosters immune escape in CRC, interacting with ZC3H12B, degrading its expression, and raising IL-6 levels. As a result, CRC proliferation and anti-apoptotic were supported, and immune escape was achieved. It is possible to regard that such a miR-155-5p in exosomes might be one of the CRC progressors and an anti-cancer target (96). MDE-mediated miR-155-5p and miR-1246 drive immune escape and pro-inflammatory signaling in CRC by regulating ZC3H12B and TGF- β cascade (194). Their consistent detection in patient exosomes underscores their value as liquid biopsy biomarkers and targets to re-sensitize tumors to therapy.

5.7 Other cancers

MDEs have shown potential to be a great inducer in numerous cancers other than lung, pancreatic, colorectal, ovarian, and breast

cancers. These exosomes promote tumorigenesis by promoting disease progression. Moreover, MDEs transfer oncogenic miRNAs and proteins that have implications for the upregulation of TME alteration-related genes (195). The upregulated genes promote glioblastoma (GBM) due to the interaction and alteration of the molecular pathways conducive to GBM growth and enhancement of therapy resistance. These exosomes were shown to promote gastric cancer (GC) by activating new metastasis-related genes (196). It seems that MDEs promote cancer progression and metastasis in all organs of a living cell, although they have not been isolated from all organs to date. In EC, miRNAs seem to play a significant role in shifting gene equilibrium to produce changes in the rate of cancer development (197).

Moreover, the altered miRNAs may act as oncogenes or tumor suppressors. Changes in the pathway characteristic of these types of miRNAs, such as cell proliferation, apoptosis, and invasion, have made the miRNAs popular in the hunt for diagnostic biomarkers and treatments (198). Mi et al. showed that M2 macrophage-derived exosomes are involved in the migration and invasion of EC. The exosomes contained the long non-coding RNA AFAP1-AS1 that inhibited miR-26a and promoted ATF2. EC was found to be able to migrate and invade due to the expression of ATF2 alone or together with the miRNA. The results showed that a therapeutic strategy could be initiated by targeting this signaling pathway, supporting more advanced EC (62). MDEs are involved in GC via the transfer of miRNAs that regulate tumor growth, invasion, and metastasis.

As the miRNAs act on the gene expression of the TME, they are one target for cancer therapeutic approaches (199). Zheng et al. discovered that TAMs activate the migration of GC through exosomes by polarizing into M2 macrophages. This exosome transfer not only involves lipid transfer but also the transfer of Apolipoprotein E (ApoE) and specific miRNAs. After the delivery of the M2-derived exosomes into the cancer cells, their migration ability is enhanced by the PI3K-AKT signaling pathway. The cancer cells from ApoE^{-/-} mice lacked the effect of the exosomes on their migration ability, and this indicates the importance of ApoE and miRNAs in driving the exosomal transfer by TAMs in the progression of cancer (200). Li et al. found that miR-16-5p loaded into exosomes derived from M1 macrophages suppresses the development of GC via the activation of T-cell-dependent immunity by targeting programmed death-ligand 1 expression in GC cells. The delivery of miR-16-5p from M1 macrophages to GC cells induced an immune response against the tumor *in vitro* and *in vivo*, specifically. Hence, the authors concluded the proposal that M1 macrophages could serve as a cellular treatment agent for GC by facilitating miR-16-5p delivery in exosomes (201). Gao et al. discovered that macrophage-derived exosomal miR-223 inhibited tumor-suppressive ubiquitin ligase substrate specificity of F-box and WD-40 repeat domain-containing 7 to promote doxorubicin resistance in GC. The transfer of miR-223 from macrophages to GC cells was found to occur using exosomes, and knockdown of miR-223 in macrophages appeared to reduce the resistance. As for clinical settings, the presence of high levels of miR-223 in both GC tissues and plasma exosomes has been linked to doxorubicin

resistance. Therefore, due to this link, targeting exosome-mediated miR-223 transfer is likely to become a helpful therapy for GC patients (202).

In GBM, miRNAs serve vital functions that facilitate the regulation of targeted genes, such as gene growth, invasion, and resistance to therapy. MiRNAs could be oversensitive or work as inhibitors of these processes, leading to their function as oncogenes or tumor suppressors that can further control major pathways and be involved in GBM (203). The role of miRNAs as biomarkers for early diagnosis, prognosis, and therapeutic targets is promising for those affected by GBM (204). Moreover, it was emphasized by Qian et al. that hypoxic glioma-derived exosomes significantly promote the M2 polarization of macrophages, resulting in enhanced glioma growth, movements, and aggressive invasion. The microRNA sequencing identified miR-1246 as the leading miRNA in H-GDEs, positively correlated with the activity of the STAT3 signaling pathway operated by the targeting recognition of TERF2IP. It was concluded that miR-1246 levels in the cerebrospinal fluid of GB patients are novel targeted chemotherapy antitumor factors (205). In other malignancies, in GC, GBM, and EC, the MDEs miRNAs, e.g., miR-223, miR-16-5p, and miR-1246, coordinate metastasis, chemoresistance, and immune modulation. The fact that they are retained regulators in a wide variety of tumor types points to their potential in becoming pan-cancer exosomal biomarkers and pan-cancer targets of therapeutic interest (206). The dynamic interplay between macrophages and the tumor microenvironment via macrophage-derived exosomes was depicted (Figure 4).

6 Limitations, safety concerns, and translational barriers of engineered MDEs

Although MDEs containing therapeutic miRNAs hold enormous potential, a series of biological and translational limitations need to be overcome before using these in clinical practice.

First, the problem of off-target effects must stay significant: the non-target tissues have the potential to absorb exosomal miRNAs, causing unwanted gene silencing and possibly a change in physiological or immune functions (207). On the same note, MDEs have inherent immunomodulatory functions, potentially leading to undesirable immunosuppression or a balance in cytokines, thus facilitating tumor immune evasion over regression (208).

In terms of bioengineering, heterogeneity of exosome isolation and miRNA loading capacity does not help with the reproducibility and dose standardization in production batches. Moreover, the large-scale production of exosomes, the absence of potent purification procedures, and the inconsistency of switching between the polarization states of the macrophages considerably affect therapy consistency (209). A further significant roadblock in the translation is related to biodistribution and clearance: when injected intravenously, MDEs are quickly taken away by the liver and the spleen, minimizing their accumulation and therapeutic efficacy to tumor properties (210, 211).

Besides, the regulatory environment of exosome-based therapeutics remains to be developed, and there is a lack of agreed quality control standards, long-term safety evaluation, and

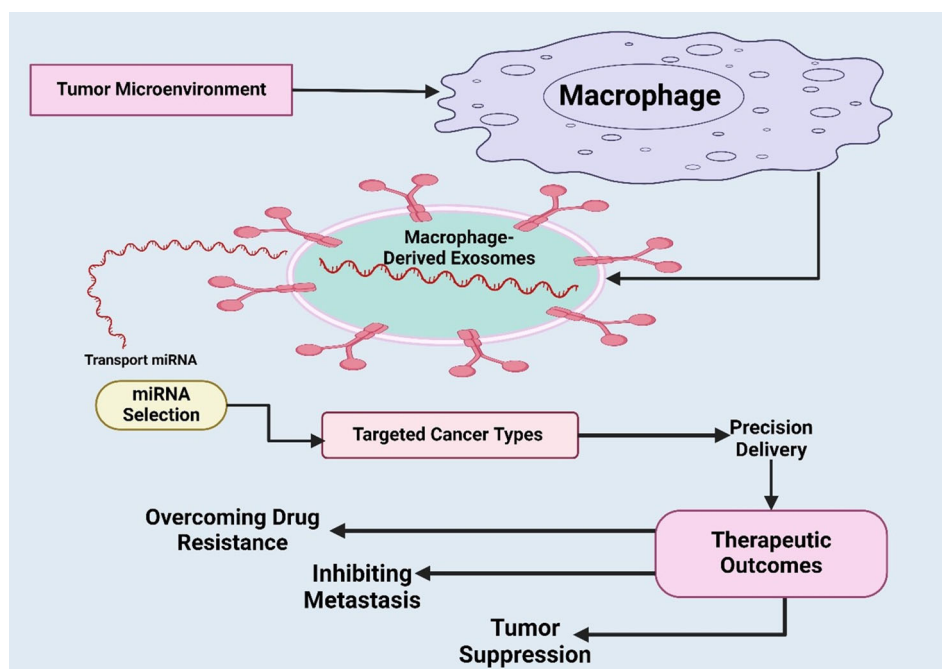


FIGURE 4

Illustration of dynamic interplay between macrophages and the tumor microenvironment via macrophage-derived exosomes were depicted. It also highlights how selected miRNAs are transported within exosomes to specific cancer targets, enabling precision delivery of therapeutic molecules. Overall, it underscores the translational significance of exosome-based strategies for targeted cancer therapy.

immunogenicity examination. Therefore, even with the promising preclinical research, the development of engineered MDE-miRNA systems into the clinic would demand stringent pharmacokinetic, toxicological, and immunological studies in a variety of animal models and controlled early-phase human trials. The standardized manufacturing protocols, specific surface engineering, and the selection of the miRNA will play a key role in the implementation of reproducible, safe, and effective MDE-based cancer therapies. Also, we have summarized the overview of macrophage-derived exosome engineering and modification for cancer therapeutics and diagnostics in Table 2.

7 Conclusion and future prospects

Collectively, these findings support clear near-term opportunities for translational studies while highlighting specific avenues for optimization and clinical validation. MDEs have a vital function in cancer biology by serving as intermediaries for communication between macrophages and tumor cells. These exosomes play a crucial role in several processes that are vital for

the advancement of cancer, such as stimulating the development of tumors, aiding in the spread of cancer to other parts of the body, causing resistance to drugs, and influencing the immune response. MDEs can greatly modify the behavior of cancer cells and the TME by transporting specific cargo, especially miRNAs. The results presented in this context demonstrate that MDEs include miRNAs that may either facilitate or impede cancer development, depending on their unique composition. For instance, the introduction of cancer-causing miRNAs via MDEs may amplify the development, invasion, and resistance to the treatment of tumors. In contrast, miRNAs that decrease tumor growth can hinder these processes. The ability to manipulate MDEs for the specific administration of therapeutic miRNAs presents new opportunities for precision medicine in the field of cancer, providing enhanced and individualized therapy alternatives.

Advances in the MDE-miRNA regimens rely on standardized work on the isolation and characterization of exosomes. Spike-in controls, cross-platform reproducibility, appropriate normalization, and common QC standards for miRNA profiling should be implemented. To be delivered safely, engineered MDEs need constructive evaluation of biodistribution, immunogenicity,

TABLE 2 Overview of macrophage-derived exosome engineering and modification for cancer applications.

Resources	M1/M2/M0	Surface engineering	Loading molecular	Loading method	Application	Study model	Reference
Lung Cancer	M1/M2	Exosome engineering	miR-30d-5p, let-7a-5p	Exosome loading	Treatment of NSCLC, Sepsis-related ALI, Autophagy induction, Apoptosis regulation	<i>in vitro</i> (A549 NSCLC cells)	(111)
Lung Cancer	M1	Exosome modification	miR-21, miR-155	Exosome loading	Diagnostic biomarker for recurrent lung cancer		(119)
Lung Cancer	M1	Exosome engineering	miR-30d-5p, SOCS1/SIRT1	Exosome loading	M1 macrophage activation, Pyroptosis regulation		(116)
Breast Cancer	M2	Exosome engineering	miR-223	Exosome loading	Promoting breast cancer cell invasion and metastasis	<i>in vitro</i> (macrophage-BC co-culture)	(138)
Breast Cancer	M2	Exosome modification	miR-146a, miR-222	Exosome loading	Tumor progression, Immune escape		(142)
Ovarian Cancer	M2	Exosome engineering	miR-221-3p	Exosome loading	Progression of EOC, Diagnostic serum biomarker	<i>in vitro</i> ; clinical (serum exosomes)	(57)
Ovarian Cancer	M2	Exosome modification	miR-29a-3p, miR-21-5p	Exosome loading	Suppression of T cells, EOC progression	<i>in vitro</i> ; clinical (patient plasma exosomes)	(58)
Hepatocellular Carcinoma (HCC)	M2	Exosome engineering	miR-125a/b	Exosome loading	Regulation of cancer stem cells, Inhibition of proliferation	<i>in vitro</i> (HCC cell lines)	(169)
Hepatocellular Carcinoma	M2	Exosome modification	miR-142, miR-223	Exosome loading	Inhibition of proliferation, Immune defense		(171)
Pancreatic Cancer	M2	Exosome modification	miR-365	Exosome loading	Chemotherapy resistance, Tumor progression	<i>in vitro</i> only (no <i>in vivo</i> xenograft)	(94)
Pancreatic Cancer	M2	Exosome modification	miR-501-3p	Exosome loading	Tumor progression, Activation of TGF- β signaling pathway	<i>in vitro</i> only (no <i>in vivo</i> xenograft)	(182)
Colorectal Cancer	M2	Exosome engineering	miR-1246	Exosome loading	Immune escape, Inflammation, Tumor progression		(191)

(Continued)

TABLE 2 Continued

Resources	M1/M2/M0	Surface engineering	Loading molecular	Loading method	Application	Study model	Reference
Colorectal Cancer	M2	Exosome engineering	miR-155-5p	Exosome loading	Immune escape, Tumor progression	<i>in vitro</i> (CRC cell lines)	(96)
Glioblastoma	M2	Exosome modification	miR-1246	Exosome loading	Tumor growth, Invasion, Therapy resistance		(205)
Gastric Cancer	M2	Exosome engineering	miR-223	Exosome loading	Drug resistance, Tumor progression	<i>in vitro</i> ; clinical (plasma/tissue association with doxorubicin resistance)	(202)
Gastric Cancer	M2	Exosome modification	miR-223	Exosome loading	Tumor progression, Metastasis	<i>in vitro</i> ; <i>in vivo</i> (Apoe ^{-/-} mice)	(200)

complement activation, thrombogenicity, and off-target effects, preferably on two vertebrates before clinical translation. Embracing these standards will make it possible to achieve a realistic, reproducible, and safe route to clinical testing of MDE-miRNA-based therapies.

Nevertheless, several critical constraints still need to be addressed to facilitate clinical translation. These include improving the precision of miRNA loading into MDEs and enhancing their tumor-specific delivery while minimizing off-target effects. Future studies should focus on optimizing ESCRT-dependent and -independent sorting pathways to enable selective and reproducible miRNA encapsulation. Parallel efforts should evaluate engineered MDEs functionalized with tumor-homing ligands or stimuli-responsive coatings in preclinical and early-phase (Phase I) clinical trials to assess biodistribution, immunogenicity, and therapeutic efficacy. Moreover, integrating multi-omics analyses with bioengineering and nanotechnology platforms could allow real-time monitoring of exosomal cargo loading and release kinetics, offering a rational framework for precision MDE-based therapeutics. Addressing these challenges through interdisciplinary strategies will accelerate the safe and effective translation of MDE-miRNA delivery systems into personalized cancer care.

Author contributions

PR: Conceptualization, Writing – review & editing, Writing – original draft, Project administration. MA: Methodology, Writing – original draft, Data curation. MB: Validation, Writing – review & editing. RM: Data curation, Writing – original draft. SS: Data curation, Writing – review & editing. SP: Formal analysis, Writing – original draft, Data curation. HA: Writing – review & editing, Formal analysis. MH: Formal analysis, Data curation, Writing – review & editing, Writing – original draft. GG: Writing – review & editing, Investigation, Conceptualization. JM: Writing – review & editing, Formal analysis, Supervision. SA: Validation, Writing – review & editing, Supervision.

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