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Review

Role of M2 macrophage-derived exosomes in cancer drug resistance via noncoding RNAs

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Abstract
This review summarizes recent findings on the role of M2 tumor-associated macrophages (TAMs) and their exosome-derived non-coding RNAs (ncRNAs) in cancer cell resistance to therapeutics. M2 TAMs promote angiogenesis, suppress immune responses, and facilitate metastasis, thereby creating a tumor-supporting microenvironment. A range of anti-tumor drugs, including 5-FU, cisplatin, and gemcitabine, are mediated by M2 exosomes, each with distinct mechanisms of action. M2 exosomes transfer drug resistance capabilities via extracellular vesicles, especially exosomes containing miRNAs, lncRNAs, and circRNAs. These exosome mediate the development of tumor drug resistance by regulating signaling pathways such as PI3K/AKT, MAPK/ERK, Wnt/β-catenin M2 exosomes can regulate cellular responses by delivering bioactive molecules, including proteins, lipids, and ncRNA, which can also modulate cellular reactions to ionizing radiation, ultraviolet light, and chemotherapeutic agents. Targeting M2 TAMs and their exosome-mediated ncRNAs may offer new strategies to overcome drug resistance in cancer.

Keywords M2 Macrophages · Exosomes · Cancer Therapeutics · Drug resistance · ncRNAs

Abbreviations

A549R	Human lung adenocarcinoma cells
BCSCs	CD24− CD44+ BC stem cells
CML LSCs	CML leukemic stem cells
DKK2	Dickkopf-related protein 2
EGFR	Epidermal growth factor receptor
GBM	Glioblastoma
HCC	Hepatocellular carcinoma
HemSCs	Hemangioma stem cells
HNSCC	Head and neck squamous cell carcinoma
LUAD	Lung adenocarcinoma cells
MM	Multiple myeloma cells
MPM	Malignant pleural mesothelioma
NSCLC	Non-small cell lung cancer
OSCC	Oral squamous cell carcinoma cells

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OS	Osteosarcoma
PDAC	Pancreatic ductal adenocarcinoma
PCa	Prostate cancer
PTEN	Phosphatase and tensin homologue
PVT1	Plasmacytoma variant translocation 1
TIMP3	Tissue inhibitor of matrix metalloproteinases 3
TNBC	Triple-negative breast cancer

1 Introduction

Cancer is a devastating disease that significantly impacts global health, with millions of new cases and deaths reported annually. Despite considerable progress in treatment modalities, including surgery, radiation therapy, chemotherapy, and immunotherapy, the mortality rate remains high, and drug resistance remains a significant challenge. The tumor microenvironment (TME) plays a pivotal role in the development of drug resistance and subsequent tumor progression. Within the TME, various cell types interact dynamically, contributing to the tumor's ability to evade therapeutic interventions. Tumor-associated macrophages (TAMs) have been widely recognized for their role in promoting cancer progression and drug resistance. However, other components of the TME, such as cancer-associated fibroblasts, cancer stem cells, regulatory T cells (Tregs), and others, also play crucial roles in shaping the tumor's response to treatment [1]. Understanding the complex interactions within the TME is essential for developing more effective therapeutic strategies to combat cancer [2, 3].

Macrophage extracellular vesicles (EVs) are nanoscale membrane vesicles secreted by macrophages. These EVs play a crucial role in cancer development, as they can carry various molecules, including proteins, RNA, and DNA, from one cell to another, thereby influencing cell function [4, 5].

While M1 macrophages are pro-inflammatory and stimulatory for immune activation [6, 7], M2 macrophages are associated with anti-inflammatory and tissue repair functions [8]. As the tumor develops, these M1 macrophages can undergo a phenotypic switch to M2 macrophages, which exhibit anti-inflammatory and protumorigenic characteristics. The M2 macrophages then contribute to tumor progression by promoting angiogenesis, suppressing immune responses, and enhancing drug resistance.M2 exosomes, a subtype of EVs, play a crucial role in mediating antitumor drug resistance [9–11].

A growing number of studies have investigated the role of M2 exosomes in mediating resistance to a wide range of antitumor drugs, including 5-Fluorouracil (5-FU), Arsenic trioxide (ATO), Bortezomib, Cisplatin, Decitabine (DCA), Docetaxel (DCT), Doxorubicin, Gefitinib, Gemcitabine, Imatinib mesylate, Paclitaxel, Propranolol, S63845, Sorafenib, Temozolomide, and Venetoclax (Fig. 1) [12]. These drugs encompass diverse therapeutic classes and mechanisms of action, yet M2 exosomes have been shown to contribute to resistance across multiple modalities. Furthermore, meta-analyses, along with experimental studies, have shown that by understanding how these exosomes interact with and influence tumor cells, we can potentially harness their unique properties to overcome drug resistance and directly deliver therapeutic agents to the site of the tumor, thereby enhancing the efficacy of cancer treatment [13].

Several gaps and challenges remain in our understanding of M2 exosome-mediated drug resistance. First, the precise molecular mechanisms underlying exosome-tumor cell interactions and the subsequent modulation of drug sensitivity are not fully elucidated. Second, the heterogeneity of exosomes, both in terms of their composition and functional effects, complicates the development of targeted therapeutic strategies. Finally, the therapeutic potential of harnessing M2 exosomes for drug delivery or sensitizing tumors to therapy remains largely unexplored.

EVs contain Non-Coding RNA (ncRNA) that play crucial roles in intercellular communication and modulation of the tumor microenvironment. Clinically, targeting M2-Exos holds promise for developing new therapeutic strategies to overcome drug resistance and improve patient outcomes in various cancers. The aim of this review is to synthesize current knowledge on the mechanisms of M2-Exos mediated drug resistance in cancer, highlight existing research gaps, and propose potential therapeutic strategies to overcome these challenges.

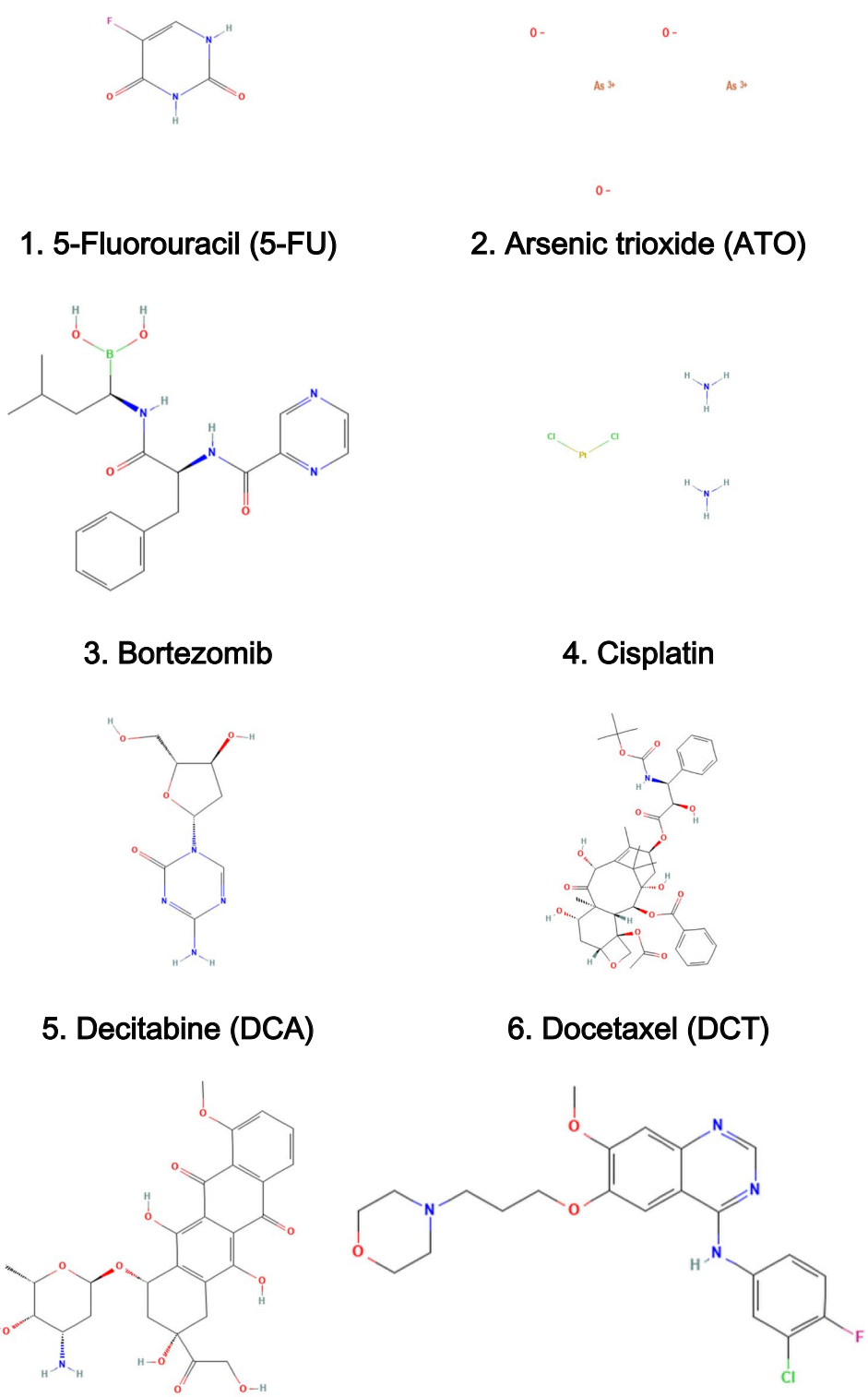
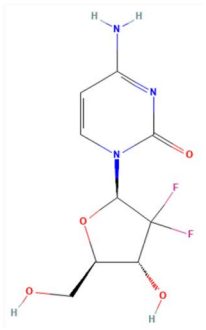


Fig. 1 Structural diagrams of 16 anti-tumor compounds

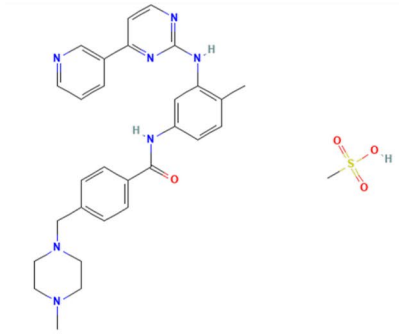
2 Method

To comprehensively investigate the role of M2 macrophage-derived microvesicles and their encapsulated non-coding RNAs (ncRNAs) in mediating cancer cell resistance to chemotherapy, a systematic literature review approach was adopted.

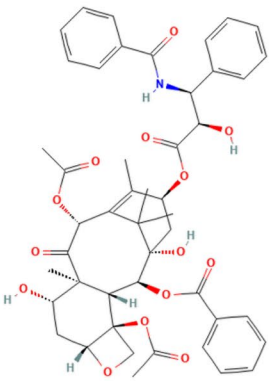
Fig. 1 (continued)



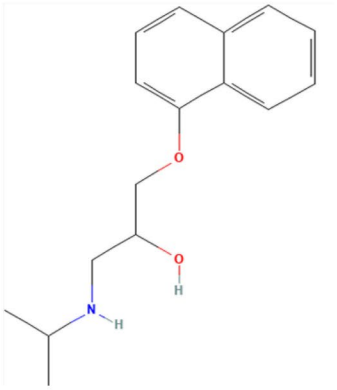
9. Gemcitabine



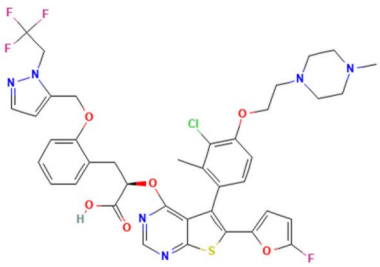
10. Imatinib mesylate



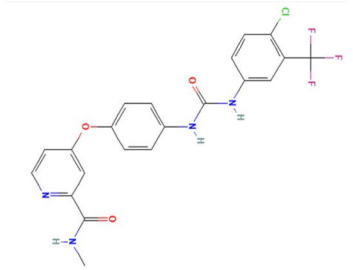
11. Paclitaxel



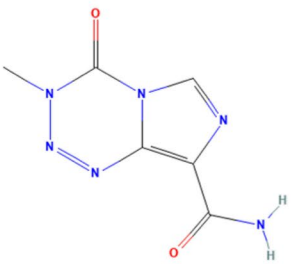
12. Propranolol



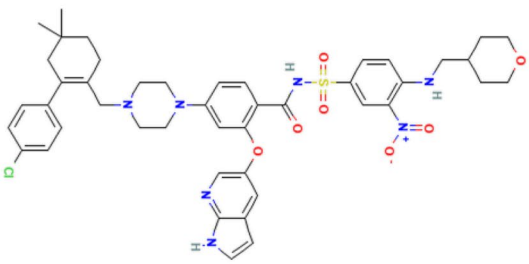
13. S63845



14. Sorafenib



15. Temozolomide



16. Venetoclax

Following rigorous selection criteria, a comprehensive electronic search was conducted across reputable databases such as PubMed, Scopus, and Web of Science, encompassing studies from the inception of research in this field up to the most recent publication date.

To supplement the electronic search, a manual review was also performed, exploring cited references and expert recommendations to ensure capture of all pertinent research. The focus was on selecting high-quality research articles that explicitly explored the relationship between M2 macrophage-derived microvesicles, their ncRNA cargo (including miRNAs, lncRNAs, circRNAs, etc.), and chemotherapy resistance in cancer cells. Inclusion criteria stipulated that studies must clearly define the association, present a well-designed methodology outlining experimental procedures and data analysis, and be peer-reviewed original research papers.

Documents that did not meet these criteria, such as conference abstracts, case reports, or non-English publications, were excluded. Upon extensive review and evaluation of the retrieved literature, the key findings, research gaps, and potential avenues for future exploration were systematically synthesized. This approach ensures a thorough and accurate portrayal of the current state of knowledge on M2 macrophage-derived microvesicles and their ncRNAs in conferring resistance to chemotherapy in cancer cells.

Different cancers present the universality or specificity regarding the use of M2-Exosomes in treatment. In glioblastoma, M2-Exos carry ncRNAs that can alter the gene expression profiles of surrounding cells, facilitating the formation of a supportive microenvironment for tumor progression. On the other hand, in pancreatic cancer, M2-Exos have been implicated in the development of drug resistance. They mediate the transfer of ncRNAs that enhance the survival and proliferative capabilities of cancer cells, making them less responsive to conventional therapies. While they share common mechanisms of action, their specific roles and therapeutic implications can vary depending on the cancer type. These will be elaborated on the main text.

3 Macrophages polarization are emerging as key players in shaping tumor drug resistance (Fig. 2)

The tumor immune microenvironment is a dynamic and intricate network comprised of diverse immune cells, among which macrophages occupy a central position. These versatile cells have the remarkable ability to differentiate into two functionally distinct phenotypes: M1 and M2. This plasticity allows them to respond appropriately to the ever-changing conditions within the tumor microenvironment [14]. Experimental studies show that when M0 macrophages, which are undifferentiated precursors, encounter specific cytokines such as Interferon-gamma (IFN-γ) or are stimulated by molecules like Lipopolysaccharide (LPS), they undergo polarization towards the M1 phenotype [15]. This polarization is characterized by the upregulation of key transcription factors such as NF-κB, STAT1, STAT5, IRF3, IRF5, and HIF-1α. The secretory profile of M1 macrophages includes Tumor Necrosis Factor-alpha (TNF-α), Interleukin-1 alpha (IL-1α), IL-1β, IL-6, IL-12, and IL-23 [16]. These cytokines not only mediate the destruction of tumor cells but also activate and recruit other immune cells to the tumor site. Chemokines also play a pivotal role in M1 mediating recruitment process, drawing in effector cells that further amplify the anti-tumor immune response [17].

M2 macrophages is tightly regulated by a complex network of transcription factors, including STAT3 [18], STAT6 [19], IRF4 [20], KLF4 [21], JMJD3 [22], PPARδ [23], PPARγ [24], c-Maf [25], and cMyc [26]. The M2 macrophages can further differentiate into distinct subtypes known as M2a, M2b, M2c, and M2d, based on the specific immunological cues they encounter within the microenvironment [27]. The M2a subtype of macrophages, induced by interleukin-4 or interleukin-13, plays a crucial role in regulating breast cancer cell dormancy and carboplatin resistance through gap junctional intercellular communication [28]. Another experimental study demonstrates that both temozolomide (TMZ)-treated and untreated GBM cells shed EVs, which can induce macrophages to adopt an M2b-like phenotype [29]. Experimental studies have reported that M2c attenuates DSS-induced colitis and alleviates intervertebral disc degeneration [30, 31]. However, there have been no reports specifically linking M2c and M2d macrophages with tumor-derived EVs.

Experimental studies show that the secretion of anti-inflammatory cytokines and chemokines, such as IL-10 [32], TGF-β [33], CCL1 [34], CCL17 [35], CCL18 [36], CCL22 [37], CCL24 [38], CXCL13 [39], and VEGF [40] by M2 macrophages plays a pivotal role in remodeling the microvesicle-mediated drug resistance mechanisms. These cytokines and chemokines can modulate the composition and function of microvesicles released by M2 macrophages, thereby influencing their capacity to confer drug resistance to recipient cells. IL-10 and TGF-β, known for their immunosuppressive properties, can suppress the immune response against drug-resistant cells, allowing their survival and proliferation. Additionally, these cytokines can be incorporated into microvesicles and transferred to sensitive cells, inducing resistance phenotypes

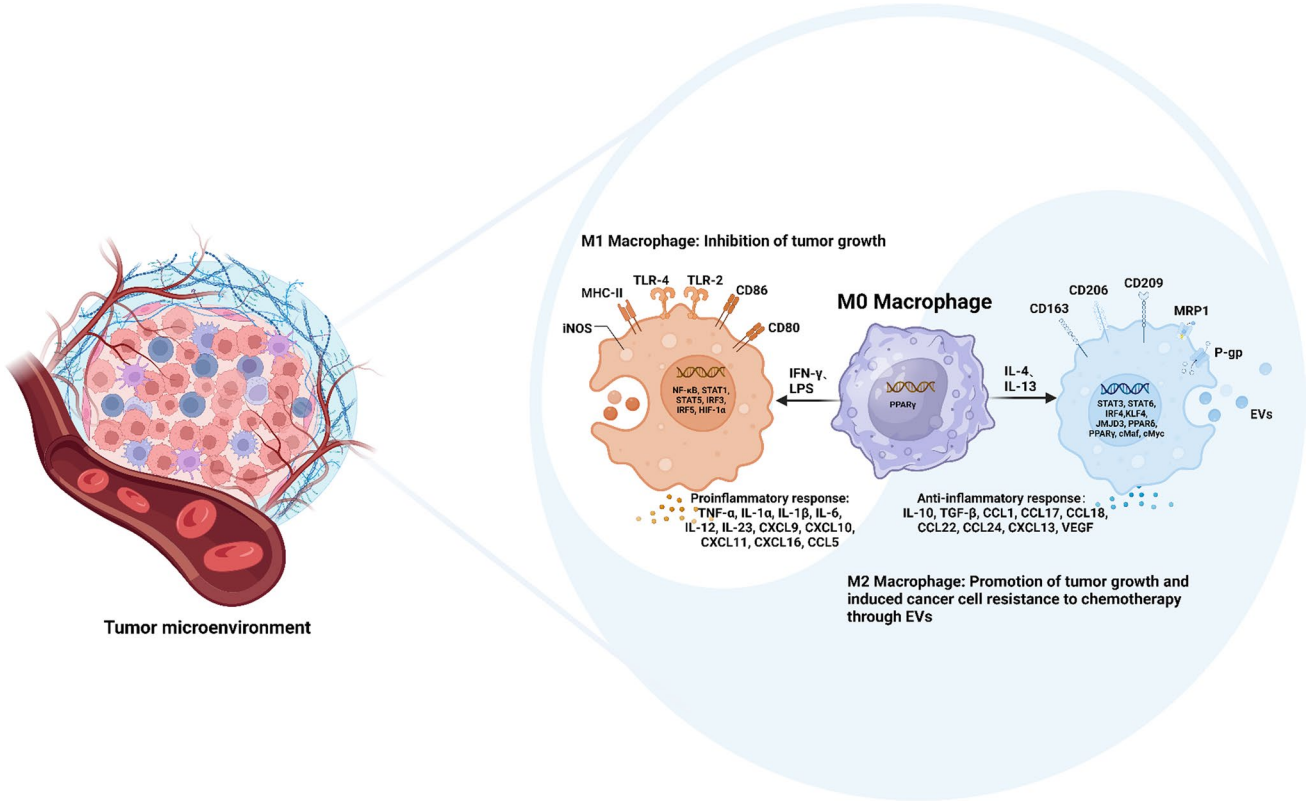


Fig. 2 Macrophage polarization in tumor microenvironment: M1 and M2 subtypes. This figure illustrates the polarization of macrophages in the tumor microenvironment, specifically highlighting the two main subtypes: M1 and M2. M1 macrophages are classically activated and exhibit anti-tumorigenic properties, while M2 macrophages are alternatively activated and promote tumor progression. The figure provides a visual representation of the distinct functional roles, cytokines and phenotypic markers associated with each subtype. The figure was created using Biorender https://www.biorender.com

[41]. The chemokines CCL1 [42], CCL17 [43], CCL18 [44], CCL22 [45], CCL24 [46], and CXCL13 [47] can also be packaged into microvesicles and act as chemotactic signals, attracting drug-resistant cells to favorable microenvironments or promoting their migration and invasion. Another experimental study presented that VEGF, a key angiogenic factor, can stimulate the formation of new blood vessels, providing a blood supply essential for the growth and survival of drug-resistant glioblastoma cells [48]. Microvesicles containing VEGF can promote angiogenesis and vascularization in the tumor microenvironment, enhancing the resistance of tumor cells to anti-angiogenic therapies.

4 The relationship between macrophage microvesicle and anticancer drug resistance

4.1 EVs derived from M2 cells (Fig. 3)

EVs are membrane-bound nanoparticles released by cells into the extracellular environment. These vesicles play crucial roles in intercellular communication, immune modulation, and various physiological and pathological processes [49]. Based on their biogenesis, size, and molecular composition, EVs are broadly classified into three main types: apoptotic bodies, exosomes, and microvesicles [50].

Apoptotic bodies, derived from cells undergoing apoptosis, are the largest among the EVs, ranging from 500 to 2000 nm in size [51]. They form as a result of cellular blebbing and are characterized by the presence of Annexin V and C3b on their surface. These markers reflect the phosphatidylserine exposure and complement activation associated with apoptosis. Apoptotic bodies typically contain cellular debris and fragments of nuclear material, reflecting their origin from dying cells.

Exosomes, on the other hand, are smaller vesicles (50–150 nm) of endocytic origin [52]. They are formed within the endosomal system and released into the extracellular space upon fusion of multivesicular bodies (MVBs) with the plasma

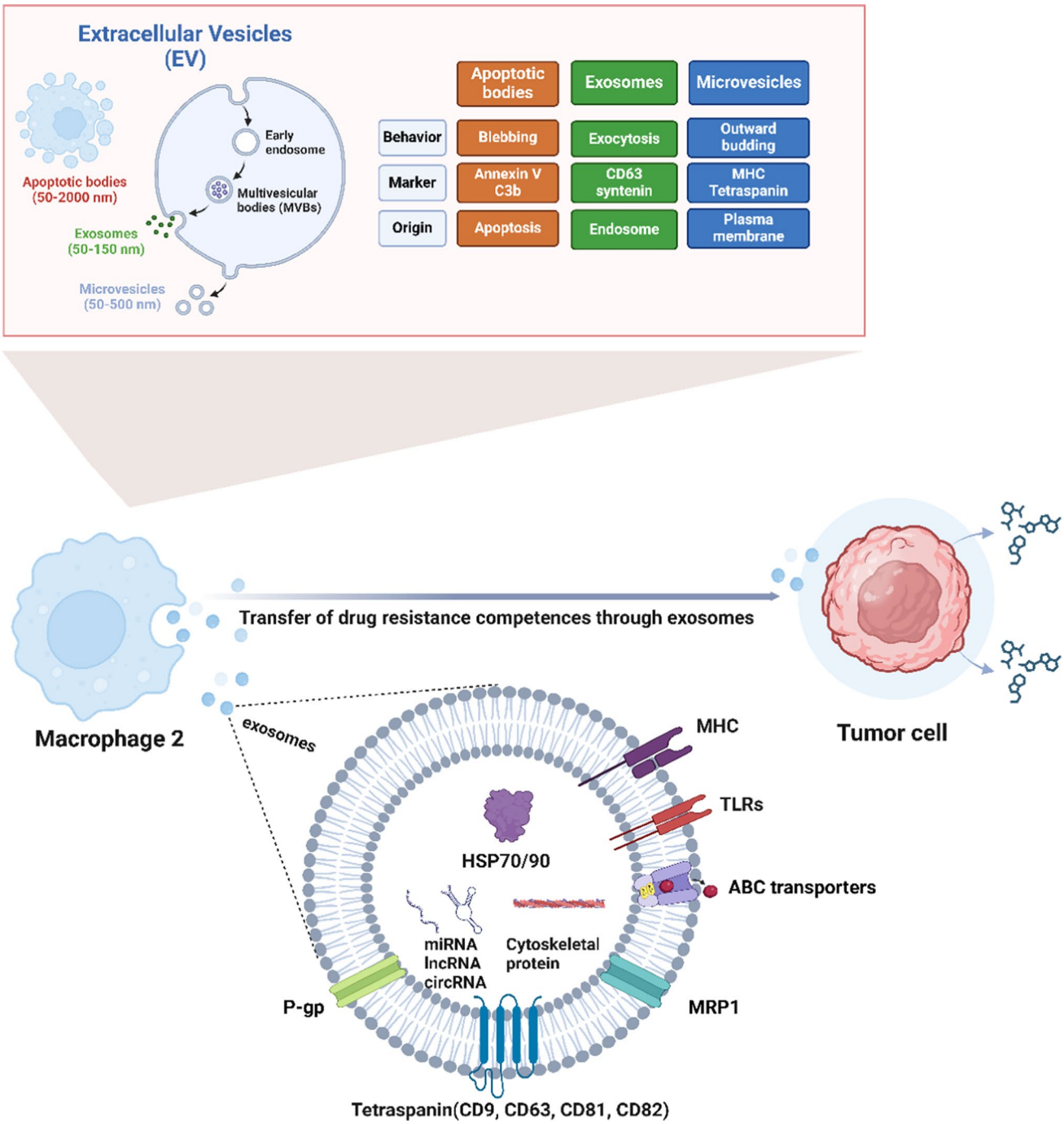


Fig. 3 Comparative analysis of macrophage 2-derived extracellular vesicles. This figure compares three types of EVs released by macrophage 2: apoptotic bodies, exosomes, and microvesicles. It highlights their role in transferring drug resistance competences, especially through exosomes bearing surface markers like p-gp, tetraspanin, and others. Additionally, the vesicular contents including HSP70/90, miRNAs, lncRNAs, and circRNAs are shown, emphasizing their significance in intercellular communication and potential impact on drug resistance mechanisms. The figure was created using Biorender https://www.biorender.com

membrane. Exosomes are enriched in tetraspanin proteins, such as CD63 and syntenin. These vesicles carry a variety of cargo, including proteins, lipids, and RNAs, reflecting their role in intercellular communication and the transfer of genetic information.

Microvesicles [53], also known as ectosomes or shedding vesicles, range in size from 50 to 500 nm. They are formed by outward budding and fission of the plasma membrane, resulting in the direct release of vesicles into the extracellular

milieu. Microvesicles are enriched in proteins associated with the plasma membrane, such as MHC (major histocompatibility complex) molecules and tetraspanins [54]. These vesicles play important roles in cell–cell interactions, immune responses, and the transfer of membrane-associated proteins and lipids.

4.2 Exosomes is the key players in the transfer of drug resistance competences

Exosomes play a pivotal role in the transfer of drug resistance competences, emerging as key mediators in intercellular communication. These nanosized vesicles, secreted by cells into the extracellular environment, encapsulate a range of biomolecules, including proteins, RNAs, and lipids.. This transfer not only endows recipient cells with enhanced resistance to chemotherapeutic agents but also contributes to the heterogeneity and adaptability of tumor cell populations [55].

The surface markers of exosomes include proteins such as p-glycoprotein (p-gp) [56], tetraspanins (CD9, CD63, CD81, CD82) [57], multidrug resistance-associated protein 1 (MRP1) [58, 59], and ATP-binding cassette (ABC) transporters etc. [60]. These markers are often enriched in exosomes derived from M2 cells, which are known to play a role in immune modulation and tissue repair [61].

When exploring the complex mechanisms of drug resistance, the role of M2-Exos cannot be ignored. Unlike traditional resistance mechanisms, such as efflux pumps actively transporting drugs out of cells to reduce intracellular drug concentration, and drug target mutations altering drug binding affinity to render them ineffective, M2-Exos provide cancer cells with a novel pathway to resistance by delivering ncRNAs that regulate gene expression and alter cellular phenotypes.

The mechanism of M2-Exos generation involves the sequential process of endocytosis, formation of early endosomes, inward budding to form MVBs, and finally, fusion with the plasma membrane for exocytosis. Once released, exosomes can interact with and be taken up by recipient cells, including tumor cells. Exosomes carry a range of biomolecules, including proteins (such as HSP70/90 [62, 63], cytoskeletal proteins [64]), RNAs (miRNA, lncRNA, circRNA), and lipids [65], which play crucial roles in mediating tumor cell drug resistance. These molecules can be transferred to recipient tumor cells, thereby affecting their drug sensitivity and survival capabilities.

RNA molecules, including miRNA, lncRNA, and circRNA, can modulate gene expression to influence drug resistance in tumor cells. These RNAs are transferred to recipient cells and interact with target mRNAs to repress or enhance the expression of specific genes. This regulation can impact drug target expression levels, drug-metabolizing enzyme activity, and processes such as apoptosis and autophagy, leading to reduced drug sensitivity in tumor cells. Lastly, lipids also contribute to tumor cell drug resistance.

Exosome-carried lipids can affect cell membrane fluidity and permeability, influencing drug uptake and efflux. Additionally, specific lipid molecules can act as signaling molecules. Lipid metabolic alterations in cancer cells have been recognized as relevant players in tumor growth and proliferation, and some of these metabolic changes are reported to induce drug resistance traits that severely hinder cancer treatment [66].

4.3 Crosstalk of signaling pathways mediated by M2-exosome ncRNAs in recipient tumor cells (Fig. 4)

Firstly, crosstalk of signaling pathways mediated by upregulation M2-exosome ncRNAs in recipient tumor cells is a complex and multifaceted process that plays a pivotal role in the development and progression of drug resistance in cancer [67]. Once internalized, these ncRNAs modulate various signaling pathways within the recipient cells, leading to altered gene expression patterns and cellular responses that confer resistance to therapeutic agents. The miRNAs exhibit distinct mechanisms of action in various cancer types.T miR-21 and miR-21-5p, are upregulated in lung Cancer Cells and are associated with multiple resistance mechanisms [68]. Preclinical evidence further suggests that miR-21 activates the mTOR/β-catenin/CDK6 and STAT3/miR-21/PDCD4 pathways, both of which contribute to drug resistance [65, 66]. miR-21-5p, on the other hand, promotes sorafenib resistance and Hepatocellular Carcinoma (HCC) progression by upregulating autophagy through the USP42-SIRT7 axis [68]. Additionally, miR-21-5p may exert its effects by targeting PTEN and TIMP3, as well as through resistance to S63845 and Venetoclax via MCL-1 and BCL-2 expression [69]. miR-27a-3p promotes TMZ resistance in GBM by reducing BTG2 expression and sensitizes OS cells to Taxol by restoring Fbxw7 [70]. miR-145 binds to and suppresses HDAC11, whose upregulation contributes to drug resistance in sorafenib-resistant and metastatic HCC cells [71]. miR-155 exerts its antitumor effects by targeting multiple genes and pathways, including TSPAN5, PSMβ5 3′UTR mRNA, and the Nrf2 signaling pathway [72]. miR-186-5p is involved in drug resistance through its interaction with the TWIST1 axis and the METTL3/LINC00662/miR-186-5p pathway [73]. The downregulation of miR-186-5p may contribute to the proliferation and drug resistance of glioblastoma cells by increasing Twist1 expression [74].

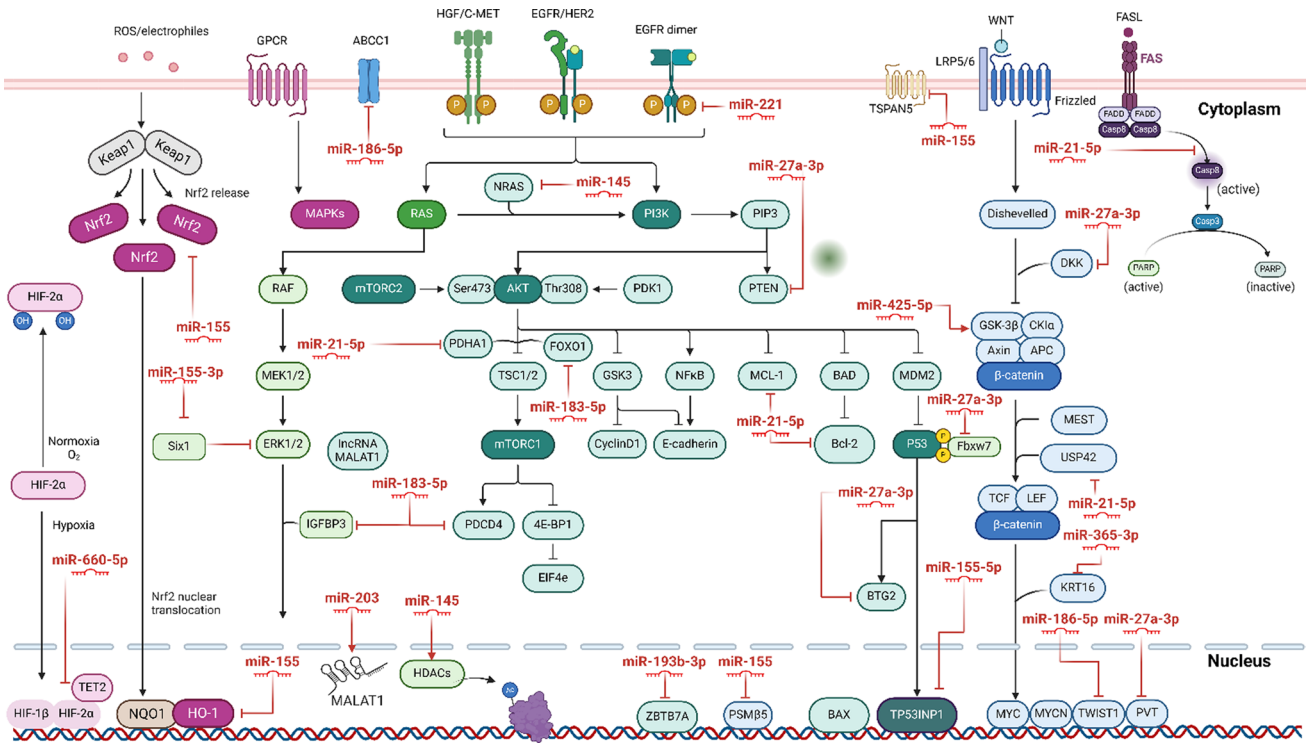


Fig. 4 Crosstalk map of M2 exosome miRNAs-mediated drug resistance in tumor cells. This figure presents a crosstalk map illustrating the complex interactions between M2 exosome miRNAs and various signaling pathways in tumor cells that mediate drug resistance. The map highlights the key miRNAs involved and their regulatory roles in modulating cellular responses to therapeutic agents. The figure was created using Biorender https://www.biorender.com

In addition to miRNAs, lncRNAs such as SBF2-AS1 and lncRNA SNHG7 also play a role in drug resistance by modulating signaling pathways. SBF2-AS1 promotes TMZ resistance through the upregulation of XRCC4 and enhanced DSB repair [75]. lncRNA SNHG7, on the other hand, is involved in the PI3K/AKT pathway, which is frequently deregulated in cancer and contributes to drug resistance [76].

On the other hand, the crosstalk of signaling pathways is mediated by the downregulation of M2-exosome ncRNAs in recipient tumor cells that exhibit chemotherapy resistance. Specifically, the downregulation of let-7d-5p contributes to the development of resistance to FTD. These interactions highlight the intricate network of crosstalk that exists between ncRNAs and their target genes or proteins, leading to the emergence of drug resistance in cancer.

4.4 M2-Exos-ncRNAs driving cancer cell resistance (Table 1)

These tiny yet mighty molecules, originating from tumor-associated macrophages with an M2 phenotype, are increasingly recognized as critical mediators in conferring resistance to cancer cells. Carried within exosomes and shuttled between cells, these ncRNAs hold the potential to profoundly influence the response of tumors to therapeutic interventions, posing a significant challenge in the clinical management of cancer. Unraveling the mysteries of M2-TAM-Exos-ncRNAs promises to open new avenues for therapeutic strategies. Understanding their role in driving cancer cell resistance could ultimately lead to improved outcomes for patients with this devastating disease.

4.4.1 miR-21

In various cancers, including head and neck, gastric, ovarian, bladder, and glioblastoma, miR-21 has been shown to promote chemoresistance by targeting specific pathways within cancer cells. For example, in ovarian cancer, miR-21 regulates macrophage polarization, promoting an M2 phenotype that confers chemoresistance to cancer cells [107]. In bladder cancer, miR-21 is contained within oncogenic EVs derived from M2 TAMs, promoting cisplatin resistance and malignant properties in cancer cells [69].

Table 1 Summary of key studies on M2-Exos-ncRNAs driving cancer cell resistance

Exosomal ncRNAs	Target cells or molecules	Biological function	Resistance mechanism	Resistance drugs	References
miR-21↑	Bladder cancer	Promoted migration, and tumor-sphere generation in BCa cells	mTOR/β-catenin/CDK6	Cisplatin	[69]
miR-21↑	Glioblastoma cells PDCD4	Promoting oncogenic phenotypes and M2 polarization	STAT3/miR-21/PDCD4	Temozolomide	[77]
miR-21-5p↑	Pancreatic cancer cells BTG2	miR-21-5p enhances the invasiveness of pancreatic cancer cells by promoting proliferation and invasion and attenuating gemcitabine-induced apoptosis	DSCR9/miR-21-5p/BTG2 axis	Gemcitabine	[70]
miR-21-5p↑	HCC cells USP42	miR-21-5p was found to promote autophagy	miR-21-5p promotes sorafenib resistance and HCC progression by upregulating autophagy through the USP42-SIRT7 axis	Sorafenib	[78]
miR-21-5p↑	GC cell line SGC7901 PTEN/TIMP3	Suppressing miR-21-5p expression sensitized SGC7901/DOX cells to DOX	miR-21-5p may exert its effects by targeting PTEN and TIMP3	Doxorubicin	[79]
miR-21-5p↑	Myeloma cells/pMSCs MCL-1/BCL-2	Dysregulation in multiple myeloma	Resistance to S63845 and venetoclax through MCL-1 and BCL-2 expression	S63845 Venetoclax	[80]
miR-21-5p↑	SKOV3 OC cells PDHA1	Promotes glycolysis and inhibits the chemosensitivity of the progenitor SKOV3 cells	miR-21-5p/PDHA1 axis	Cisplatin	[81]
miR-21-5p↑	HCC cells FASLG	Suppresses the sensitivity of HCC cells to cisplatin treatment	The molecular mechanism underlying the effect of miR-21-5p on cisplatin sensitivity involves the direct targeting of FASLG	Cisplatin	[71]
miR-27a-3p↑	GBM cells BTG2	Regulates TMZ resistance in GBM	Reduction in BTG2 expression promotes TMZ resistance in GBM	Temozolomide	[82]
miR-27a-3p↑	OS cells Fbxw7	Regulates the sensitivity of OS cells to Taxol	Blocking miR-27a-3p sensitizes OS cells to Taxol by restoring Fbxw7	Taxol	[83]
miR-27a-3p↑	HemSCs DKK2	Reduces the sensitivity of HemSCs to propranolol	miR-27a-3p directly targets DKK2, leading to its downregulation in HemSCs	Propranolol	[72]
miR-27a-3p↑	HepG2 and PLC cells	miR-27a-3p significantly enhances the inhibitory and apoptotic effects of cisplatin in HCC cells	PI3K/Akt signaling pathway	Cisplatin	[84]
miR-145↑	NSCLC cells NRAS/MEST	Enhance the sensitivity of gefitinib-resistant NSCLC cells to gefitinib treatment	miR-145-5p-NRAS/MEST axis	Gefitinib	[85]
miR-145↓	HCC Cells HDAC11	Functions as a tumor suppressor by directly targeting and inhibiting HDAC11 expression	miR-145-5p directly binds to and suppresses HDAC11. HDAC11 upregulation in sorafenib-resistant and metastatic HCC cells contributes to drug resistance	Sorafenib	[86]
miR-155↑	TNBC cells and BCSCs TSPAN5	Overexpression of miR-155 increases the number of CD24− CD44+ CSCs, DCA resistance, and tumor clone formation, while knockdown of miR-155 inhibits these effects	TSPAN5 is a direct target gene of miR-155, and overexpression of TSPAN5 abrogates the effect of miR-155 in promoting stemness and DCA resistance in BC cells	Decitabine (DCA)	[73]
miR-155↑	MM cells PSMβ5	miR-155 downregulation in bortezomib-resistant MM cells may contribute to their resistance phenotype	miR-155 exerts its antitumor effects involves the targeting of PSMβ5 3′UTR mRNA, leading to reduced proteasome activity	Bortezomib	[74]

Table 1 (continued)

Exosomal ncRNAs	Target cells or molecules	Biological function	Resistance mechanism	Resistance drugs	References
miR-155↑	A549R cells Nrf2, NQO1, and HO-1, as well as the Bcl-2/Bax	Increasing cell survival, colony formation, and cell migration, while decreasing cellular apoptosis	Nrf2 signaling pathway	Arsenic trioxide (ATO)	[87]
miR-155-3p↑	Glioma cells Six1	miR-155-3p modulates these cellular processes, promoting glioma progression and chemoresistance	The downregulation of Six1 expression by miR-155-3p confers resistance to temozolomide	Temozolomide	[88]
miR-155-5p↑	Breast cancer cells TP53INP1	Resistance to paclitaxel-induced apoptosis	Promotes paclitaxel resistance by targeting TP53INP1	Paclitaxel	[89]
miR-186-5p↑	MPM cells TWIST1	Affected 3D anchorage-independent growth, cisplatin resistance, invasion, and bioenergetics of the MPM cell	miR-186-5p/TWIST1 axis	Cisplatin	[90]
miR-186-5p↑	TNBC cells	Regulating docetaxel resistance in TNBC	METTL3/LINC00662/miR-186-5p pathway	Docetaxel (DCT)	[91]
miR-186-5p↓	Glioblastoma cells Twist1	Increased the proliferation and TMZ resistance of glioblastoma cells	Downregulation of miR-186-5p may contribute to the proliferation and drug resistance of glioblastoma cells by increasing Twist1 expression	Temozolomide (TMZ)	[92]
miR-186-5p↑	NSCLC cells ABCC1	Enhances cisplatin resistance in NSCLC	By sponging miR-186-5p, circ_0076305 indirectly enhances ABCC1 expression, leading to increased DDP efflux and resistance	Cisplatin	[93]
miR-365↑	Glioma cells PVT1	Overexpression of miR-365 inhibit glioma stemness, proliferation, migration, invasion, and resistance to chemotherapy (TMZ)	PVT1/miR-365/ELF4/SOX2 axis	Temozolomide	[94]
miR-365-3p↑	OSCC cells KRT16	miR-365-3p regulates migration, invasion, metastasis, and chemoresistance in OSCC cells	Depletion of KRT16 leads to inhibition of downstream signaling pathways (Src/STAT3/FAK/ERK) and enhances the cytotoxic effects of chemotherapy (5-FU) in OSCC cells	5-FU	[95]
miR-365↑	PDAC cells	miR-365 impairs the activation of gemcitabine in PDAC cells	miR-365 upregulates the triphospho-nucleotide pool and induces cytidine deaminase, leading to gemcitabine inactivation	Gemcitabine	[96]
miR-183-5p↑	PCa cells FOXO1/IGFBP3/PDCD4	Decrease the efficacy of DCT in PCa cells when overexpressed	Downregulation of target molecules (e.g., FOXO1, IGFBP3, PDCD4) and the activation of mediators (e.g., PPP2CB, INSIG1) that contribute to reduced DCT sensitivity	Docetaxel (DCT)	[97]
miR-193b-3p↑	TCam-2 cells ZBTB7A	Enhances the viability of TCam-2 cells in the presence of cisplatin by regulating cell apoptosis and the cell cycle	miR-193b-3p targets the gene ZBTB7A, which in turn decreases apoptosis and promotes cell cycle progression	Cisplatin	[98]
miR-203↓	GBM cells lncRNA MALAT1	Mediating TMZ resistance in GBM cells	MALAT1 confers TMZ resistance in GBM patients through its regulatory effects on the miR-203/TS axis	Temozolomide	[76]
miR-425-5p↓	PCa cells GSK3β	miR-425-5p played a positive role in sensitizing PCa cells to cisplatin	Resistance to cisplatin in PCa cells was partially attributed to the downregulation of miR-425-5p and the subsequent upregulation of GSK3β	Cisplatin (DDP)	[99]

Table 1 (continued)

Exosomal ncRNAs	Target cells or molecules	Biological function	Resistance mechanism	Resistance drugs	References
miR-501-3p↑	Glioma cells MYCN	It suppresses cell growth and invasion while promoting apoptosis in cisplatin-resistant glioma cells	miR-501-3p inhibits MYCN expression through post-transcriptional regulation	Cisplatin	[100]
miR-660-5p↑	CML LSCs TET2/EPAS1	Leads to downregulation of their targets TET2 and EPAS1, conferring Imatinib resistance to LSCs	Decrease the sensitivity of CML LSCs to TKIs by downregulating TET2 and EPAS1	Imatinib mesylate	[101]
miR-92a-3p↑	LUAD cells	Regulates the apoptotic threshold and proliferative capacity of tumor cells, specifically KRAS-mutated LUAD cells	Target genes or pathways involved in apoptosis and cell proliferation	Cisplatin	[102]
SBF2-AS1↑	GBM cells	lncSBF2-AS1 promotes TMZ resistance in GBM cells	Upregulation of XRCC4 and enhanced DSB repair, ultimately promoting TMZ resistance	Temozolomide	[103]
SNHG7↑	LUAD cells ATG5/ATG12	Enhances docetaxel resistance via Inducing autophagy and macrophage M2 polarization	PI3K/AKT pathway	Docetaxel	[104]
Let-7d↓	Colorectal cell	Determining the response of colorectal cancer cells to FTD	The downregulation of let-7d-5p appeared to contribute to the development of resistance to FTD	Trifluridine (FTD)	[105]
miR-221↑	Glioblastoma cells EGFR	Acts as a negative regulator of EGFR expression	This reduction in EGFR expression renders the cells less sensitive to anti-EGFR agents	Temozolomide	[106]

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Targeting miR-21 enhances doxorubicin sensitivity in triple-negative breast cancer by reversing P-gp-mediated drug resistance through phosphatase and tensin homolog (PTEN) up-regulation [108]. Additionally, M2-derived miR-21-enriched exosomes induce temozolomide resistance in glioblastoma cells by targeting PDCD4, promoting oncogenic phenotypes and M2 polarization [77].

M2-associated miR-21-5p has also been implicated in the development of chemotherapy resistance in various cancer types. In pancreatic cancer, miR-21-5p enhances cell invasiveness, promotes proliferation, and attenuates gemcitabine-induced apoptosis by targeting BTG2 [70]. In hepatocellular carcinoma (HCC), miR-21-5p promotes sorafenib resistance and autophagy through the USP42-SIRT7 axis [78]. Additionally, miR-21-5p upregulation in gastric cancer cell line SGC7901 contributes to doxorubicin resistance by targeting PTEN and TIMP3 [79]. In myeloma cells, miR-21-5p dysregulation confers resistance to S63845 and venetoclax through MCL-1 and BCL-2 expression [80]. Furthermore, in ovarian cancer (OC) cells, miR-21-5p promotes glycolysis and inhibits cisplatin sensitivity by targeting PDHA1 [81]. Similarly, in HCC cells, miR-21-5p suppresses cisplatin sensitivity by directly targeting FASLG [71]. These findings suggest that macrophage-derived miR-21-5p contributes to chemotherapy resistance by targeting various tumor suppressor genes, leading to enhanced cell survival, proliferation, invasion, and autophagy, ultimately reducing the efficacy of chemotherapeutic agents. The mechanism of miR-21-induced chemoresistance often involves the repression of tumor suppressors or the activation of oncogenic pathways, leading to enhanced cancer cell survival and proliferation.

4.4.2 miR-27

In glioblastoma multiforme (GBM) cells, upregulation of miR-27a-3p leads to resistance against temozolomide (TMZ) by targeting BTG2, a tumor suppressor gene. Reduction in BTG2 expression promotes TMZ resistance, highlighting a potential mechanism by which miR-27a-3p confers chemoresistance in GBM [82]. In osteosarcoma (OS) cells, miR-27a-3p regulates sensitivity to Taxol (paclitaxel) chemotherapy. Blocking miR-27a-3p sensitizes OS cells to Taxol by restoring the expression of Fbxw7, a gene that plays a crucial role in regulating cell cycle progression and apoptosis. This suggests that miR-27a-3p-mediated downregulation of Fbxw7 contributes to chemoresistance in OS [83]. Furthermore, in hemangioma stem cells (HemSCs), miR-27a-3p reduces sensitivity to propranolol, a non-selective beta-blocker commonly used in the treatment of various vascular malformations [72]. Moreover, miR-27a-3p directly targets DKK2, leading to its downregulation in HemSCs, thereby reducing the therapeutic efficacy of propranolol. Additionally, in HepG2 and PLC hepatocellular carcinoma (HCC) cells, miR-27a-3p significantly enhances the inhibitory and apoptotic effects of cisplatin through inhibiting PI3K/Akt pathway [84]. Nonetheless, it is evident that miR-27a-3p plays a crucial role in modulating the response of HCC cells to cisplatin chemotherapy. Taken together, these findings suggest that macrophage-derived miR-27a-3p contributes to chemotherapy resistance by targeting various genes involved in cell cycle regulation, apoptosis, and drug metabolism.

4.4.3 miR-145

miR-145 has been shown to play a role in chemotherapy drug resistance in non-small cell lung cancer (NSCLC) and hepatocellular carcinoma (HCC) cells. Experimental studies show that in NSCLC cells, upregulation of miR-145 enhances the sensitivity of gefitinib-resistant cells to gefitinib treatment by targeting the NRAS/MEST axis [85]. This suggests that miR-145 may overcome gefitinib resistance in NSCLC by regulating the expression or activity of NRAS and MEST, which are involved in cell survival and proliferation pathways. In HCC cells, downregulation of miR-145 contributes to sorafenib resistance by directly targeting and inhibiting HDAC11 expression [86]. HDAC11 upregulation in sorafenib-resistant and metastatic HCC cells promotes drug resistance. Therefore, the loss of miR-145 expression may lead to the deregulation of HDAC11, resulting in the development of sorafenib resistance in HCC.

4.4.4 miR-155

miR-155 contributes to chemotherapy resistance in various cancer types by targeting different genes involved in cell survival, proliferation, and apoptosis. The upregulation of miR-155 may promote drug resistance by inhibiting the expression of tumor suppressor genes or activating oncogenic signaling pathways. In triple-negative breast cancer (TNBC) cells and breast cancer stem cells (BCSCs), overexpression of miR-155 is associated with increased stemness, resistance to decitabine (DCA), and tumor clone formation. TSPAN5 is identified as a direct target gene of miR-155, and its overexpression abrogates the effect of miR-155 in promoting stemness and DCA resistance [73]. This suggests

that miR-155 contributes to chemoresistance in TNBC and BCSCs by targeting TSPAN5. In multiple myeloma (MM) cells, downregulation of miR-155 may contribute to bortezomib resistance [74]. miR-155 exerts its antitumor effects by targeting PSMβ5 3′UTR mRNA, leading to reduced proteasome activity. Therefore, the loss of miR-155 expression in bortezomib-resistant MM cells may confer resistance to this chemotherapeutic agent. In lung cancer cells (A549R), miR-155 upregulation is associated with increased cell survival, colony formation, and cell migration, while decreasing cellular apoptosis. This effect is mediated through the Nrf2 signaling pathway, which regulates the expression of antioxidant and detoxifying enzymes such as NQO1 and HO-1, as well as the Bcl-2/Bax apoptotic pathway. miR-155 upregulation may confer resistance to arsenic trioxide (ATO) chemotherapy by activating the Nrf2 signaling pathway [87]. In glioma cells, miR-155-3p promotes tumor progression and chemoresistance by modulating various cellular processes. The downregulation of Six1 expression by miR-155-3p confers resistance to temozolomide, suggesting that miR-155-3p contributes to chemoresistance in glioma by targeting Six1 [88]. Lastly, in breast cancer cells, miR-155-5p promotes resistance to paclitaxel-induced apoptosis by targeting TP53INP1 [89]. TP53INP1 is a tumor suppressor gene that regulates apoptosis and autophagy. miR-155-5p upregulation may lead to the downregulation of TP53INP1, thereby conferring resistance to paclitaxel chemotherapy.

4.4.5 miR-186

miR-186-5p contributes to chemotherapy resistance in different cancer types by targeting various genes and pathways involved in cell survival, proliferation, and drug efflux. Upregulation or downregulation of miR-186-5p may lead to the deregulation of oncogenes or tumor suppressor genes, conferring resistance to cisplatin, docetaxel, and temozolomide chemotherapy.

In MPM cells, upregulation of miR-186-5p affects 3D anchorage-independent growth, cisplatin resistance, invasion, and bioenergetics by targeting TWIST1. The miR-186-5p/TWIST1 axis plays a crucial role in cisplatin resistance, suggesting that miR-186-5p contributes to chemoresistance in MPM by regulating TWIST1 expression [90]. In TNBC cells, miR-186-5p regulates docetaxel resistance through the METTL3/LINC00662/miR-186-5p pathway [91]. Although the specific mechanism by which miR-186-5p confers docetaxel resistance is not fully elucidated, this pathway represents a potential target for overcoming chemoresistance in TNBC. In glioblastoma cells, downregulation of miR-186-5p increases the proliferation and temozolomide (TMZ) resistance by increasing Twist1 expression [92]. This suggests that the loss of miR-186-5p expression may contribute to chemoresistance in glioblastoma by deregulating Twist1, a known oncogene involved in cancer progression and drug resistance. In NSCLC cells, miR-186-5p enhances cisplatin resistance by indirectly increasing ABCC1 expression through sponging interactions with circ_0076305. This leads to increased cisplatin efflux and resistance, indicating that miR-186-5p plays a role in cisplatin resistance in NSCLC by regulating drug transport proteins [93].

4.4.6 miR-365

miR-365 has been implicated in the development of chemotherapy drug resistance in glioma, oral squamous cell carcinoma (OSCC), and pancreatic ductal adenocarcinoma (PDAC) cells. In glioma cells, overexpression of miR-365 inhibits glioma stemness, proliferation, migration, invasion, and resistance to chemotherapy with temozolomide (TMZ). The mechanism involves the PVT1/miR-365/ELF4/SOX2 axis [94], suggesting that miR-365 may target PVT1 to regulate the expression of downstream genes involved in glioma progression and chemoresistance. While macrophages were not directly studied in this context, it is known that miRNAs can be secreted by various cell types, including macrophages, and influence the behavior of other cells in the tumor microenvironment. In OSCC cells, miR-365-3p regulates migration, invasion, metastasis, and chemoresistance [95]. Depletion of the miR-365-3p target gene KRT16 leads to the inhibition of downstream signaling pathways (Src/STAT3/FAK/ERK) and enhances the cytotoxic effects of chemotherapy with 5-fluorouracil (5-FU). Again, while the direct involvement of macrophages in this mechanism remains to be elucidated, it is plausible that miR-365-3p secreted by macrophages or other immune cells may influence the chemoresistance of OSCC cells by targeting KRT16. In PDAC cells, miR-365 impairs the activation of gemcitabine by upregulating the triphosphonucleotide pool and inducing cytidine deaminase [96], leading to gemcitabine inactivation. This suggests that miR-365 may confer resistance to gemcitabine treatment in PDAC by directly interfering with its activation mechanism. Macrophages, as key components of the tumor microenvironment, may contribute to this resistance by secreting miR-365 or other factors that regulate its expression in PDAC cells.

4.4.7 Other M2-Exos-miRNAs

In prostate cancer (PCa) cells, miR-183-5p overexpression decreases the efficacy of docetaxel (DCT) by downregulating target molecules such as FOXO1, IGFBP3, and PDCD4, and activating mediators like PPP2CB and INSIG1, which contribute to reduced DCT sensitivity [97]. While the direct involvement of macrophages remains to be elucidated, it is plausible that miR-183-5p secreted by macrophages or other immune cells may influence the chemoresistance of PCa cells by targeting these molecules. In testicular cancer (TCam-2) cells, miR-193b-3p enhances cell viability in the presence of cisplatin by regulating apoptosis and the cell cycle. The miRNA targets the gene ZBTB7A, which in turn decreases apoptosis and promotes cell cycle progression [98]. In melanoma, M2 macrophages promote drug resistance through various mechanisms, including the secretion of exosomal contents. We found that miRNAs, specifically miR-199-5p and miR-204-5p, can overcome this resistance by targeting melanoma cells and disrupting the recruitment of pro-tumoral macrophages, offering a potential new therapy for metastatic melanoma [75]. In glioblastoma multiforme (GBM) cells, the lncRNA MALAT1 confers resistance to temozolomide (TMZ) through its regulatory effects on the miR-203/TS axis [76]. While the specific role of macrophages in this mechanism remains to be investigated, it is conceivable that MALAT1 secreted by macrophages or other immune cells may influence the chemoresistance of GBM cells. In another study, miR-425-5p played a positive role in sensitizing PCa cells to cisplatin by targeting GSK3β [99]. Resistance to cisplatin in PCa cells was partially attributed to the downregulation of miR-425-5p and the subsequent upregulation of GSK3β. Macrophages may contribute to this resistance by secreting factors that regulate the expression of miR-425-5p and GSK3β in PCa cells. In glioma cells, miR-501-3p suppresses cell growth and invasion while promoting apoptosis in cisplatin-resistant cells by inhibiting MYCN expression through post-transcriptional regulation [100]. In chronic myeloid leukemia stem cells (CML LSCs), miR-660-5p confers resistance to imatinib mesylate by downregulating TET2 and EPAS1 [101]. While the direct role of macrophages in this mechanism remains unclear, it is possible that miR-660-5p secreted by macrophages or other immune cells may contribute to imatinib resistance in CML LSCs by targeting these genes. In lung adenocarcinoma (LUAD) cells with KRAS mutations, miR-92a-3p regulates the apoptotic threshold and proliferative capacity of tumor cells, potentially contributing to cisplatin resistance [102]. Macrophages may influence the expression of miR-92a-3p in LUAD cells and thereby modulate their sensitivity to cisplatin treatment.

4.4.8 M2-Exos-lncRNA

Insights derived from experimental studies and clinical trials indicate that, in GBM cells, the lncRNA SBF2-AS1 promotes TMZ resistance by upregulating XRCC4 and enhancing double-strand break (DSB) repair [103]. While the involvement of macrophages in this mechanism is speculative, it is conceivable that lncRNAs secreted by macrophages or other immune cells may influence the chemoresistance of GBM cells by regulating DSB repair pathways. Exosomal lncRNA SNHG7 enhances docetaxel resistance in lung adenocarcinoma (LUAD) cells by inducing autophagy and macrophage M2 polarization [104]. SNHG7 is overexpressed in docetaxel-resistant cells and promotes autophagy by stabilizing ATG5 and ATG12 genes via HuR recruitment. Additionally, SNHG7 is transmitted through exosomes from resistant to parental LUAD cells, facilitating drug resistance. SNHG7 also activates the PI3K/AKT pathway in macrophages, promoting M2 polarization through CUL4A-mediated ubiquitination and degradation of PTEN. This study implicates SNHG7 as a potential target for overcoming docetaxel resistance in LUAD, emphasizing the role of exosomal RNAs and macrophage polarization in chemotherapy resistance mechanisms.

4.5 Other M2-Exos contents driving cancer cell resistance

Other M2-derived exosomal contents, rich in TGF-β, can promote EMT and drug resistance in cancer cells. This process involves the downregulation of epithelial markers like E-cadherin and the upregulation of mesenchymal markers like vimentin and N-cadherin. EMT not only endows cancer cells with a more aggressive phenotype but also alters their metabolic pathways and drug efflux mechanisms, contributing to drug resistance. The experimental study demonstrates a promising simvastatin-based nanomedicine strategy that targets exosomal metabolism to reverse EMT and repolarize TAM from M2 to M1 phenotype, thereby overcoming drug resistance in cancer through modulation of cholesterol/lipid raft/integrin β3/FAK and cholesterol-associated LXR/ABCA1 pathways [109]. M2-derived exosomes can carry active Rho GTPase or its regulators, which can be taken up by cancer cells, leading to enhanced p21-activated kinase (PAK) activation. This, in turn, can promote cell migration, invasion, and survival pathways, making cancer cells more resistant to chemotherapeutic drugs. The experimental study further demonstrates that Rho GTPase plays a critical role in the

dual functions of matricellular protein SPON2 in the HCC microenvironment. Specifically, it activates RhoA and Rac1 via SPON2-α4β1 integrin signaling, which promotes the recruitment of M1-like macrophages. Conversely, it inactivates RhoA through SPON2-α5β1 integrin signaling, thereby inhibiting HCC cell migration [110]. HSP70/90, a significant component of M2-derived exosomal contents, functions as a molecular chaperone that aids in the folding and stabilization of drug targets, thereby shielding them from drug assault. Furthermore, M2-derived exosomes can carry HSP70/90, which can be delivered to cancer cells. These chaperones can interact with and stabilize drug resistance-related proteins, such as ABC transporters (e.g., P-glycoprotein), thereby enhancing drug efflux and reducing intracellular drug concentrations [111]. Experimental studies that cytoskeletal proteins regulate intracellular signaling pathways and transport processes, affecting drug distribution and metabolism within the cell [112].

Another M2-derived exosomal contents may promote cancer cell resistance by enhancing lipid metabolism and inducing M2-like TAM polarization. In lung adenocarcinoma, TIAM2, a hub gene identified through weighted gene co-expression network analysis, contributes to osimertinib resistance and cell motility, highlighting its potential role in driving drug resistance [113]. Recent findings indicate that palmitic acid, delivered via a poly(d,l-lactic co-glycolic acid) (PLGA) nanoparticles, can effectively repolarize M2 macrophages and reduce drug resistance in breast cancer, offering a promising new therapeutic approach [114]. Another study also demonstrates that combining doxorubicin with mitomycin C and delivering via polymer-lipid hybrid nanoparticles overcomes multidrug resistance and reduces cardiotoxicity, offering a promising strategy for aggressive cancer treatment [115].

5 Conclusion

The reviewed studies provide compelling evidence for the critical role of M2-TAMs and their exosome-derived ncRNAs in mediating cancer cell resistance to therapeutic agents. Figures 1 and 2 illustrate the polarization of macrophages in the tumor microenvironment, emphasizing the distinct functional roles and phenotypic markers of M1 and M2 subtypes. Notably, M2 macrophages, which are alternatively activated, not only promote tumor progression but also facilitate the transfer of drug resistance via exosomes, which contain HSP70/90, miRNAs, lncRNAs, and circRNAs. These vesicular contents play pivotal roles in intercellular communication and drug resistance mechanisms, as further elaborated in Fig. 3, which highlights the complex interactions between M2 exosome miRNAs and signaling pathways in tumor cells.

The mechanisms by which M2-Exos contribute to drug resistance and disease progression may differ significantly between solid tumors and hematological malignancies. In solid tumors, M2-Exos may promote the formation of a tumor-supporting microenvironment by stimulating angiogenesis, enhancing cell migration and invasion, and modulating the immune response. Conversely, in hematological cancers, M2-Exos may play a more direct role in protecting cancer cells from the effects of chemotherapeutic agents, or they may be involved in the complex interactions between cancer cells and the bone marrow microenvironment. Therapeutic strategies targeting M2-Exos must be tailored to the specific characteristics of each cancer type. For solid tumors, approaches such as localized delivery of therapeutic agents directly to the tumor site or the use of nanoparticles to specifically target M2-Exos can be explored. In hematological cancers, systemic treatments that can effectively reach and disrupt the interaction between M2-Exos and cancer cells in the bloodstream or bone marrow may be more appropriate. Furthermore, the potential side effects and toxicity profiles of treatments targeting M2-Exos may also differ between solid tumors and hematological cancers. For example, compared to hematological malignancies, treatments targeting M2-Exos in solid tumors may have less systemic impact, whereas treatments for the latter may affect the entire hematopoietic system.

Significant progress has been made in addressing the many unresolved issues surrounding the use of M2-Exos for treatment. To enhance delivery efficiency and accuracy, we can consider employing various strategies. For instance, utilizing advanced nanotechnologies such as liposomes, polymeric nanoparticles, or inorganic nanocarriers can protect ncRNA from degradation in the body's environment and precisely deliver it to target cells or tissues. In order to improve treatment specificity, we need to delve deeper into the biological characteristics and molecular mechanisms of M2-Exos to identify unique and specific targets. By designing drugs or therapies that target these specific markers, we can more precisely disrupt the functions of M2-Exos while minimizing the impact on normal cells or tissues. Additionally, combining multiple therapeutic approaches, such as combination therapy or targeted therapy, can further enhance the specificity and effectiveness of the treatment. Looking ahead, several avenues for future research emerge. Firstly, there is a pressing need to develop specific inhibitors that can effectively block the activation of M2-TAMs and the subsequent transfer of ncRNAs via exosomes. Secondly, clinical trials should be conducted to assess the efficacy and safety of these targeted therapies in overcoming drug resistance in cancer patients. Additionally, tumor cell heterogeneity is a well-recognized

feature of cancer, with implications for therapy response and resistance. Future studies could investigate how different subpopulations of tumor cells may differentially interact with TAM-derived exosomes, potentially leading to varied responses to therapeutic interventions. Besides, the tumor microenvironment is composed of a diverse array of immune cells, each with unique functions and potential interactions with exosomes. Exploring the crosstalk between TAMs, other immune cells, and tumor cells, mediated by exosomes, could reveal novel mechanisms of immune evasion, tumor progression, and therapeutic resistance.

In cancer therapy, M2 exosomes have been implicated in promoting tumor growth, metastasis, and drug resistance. By inhibiting the release or function of these exosomes, exosome inhibitors could potentially sensitize cancer cells to conventional therapies, such as chemotherapy and immunotherapy, thereby enhancing overall treatment efficacy and reducing drug resistance. Furthermore, the development of M2 exosome-based biomarkers offers a promising avenue for personalized medicine. These biomarkers could be utilized for early disease detection, patient stratification, and monitoring of treatment response. By analyzing the content of M2 exosomes, such as proteins, nucleic acids, and lipids, clinicians could gain valuable insights into the disease state and tailor treatment plans accordingly. For example, specific exosomal markers may identify patient subpopulations that are more likely to respond to certain therapies, allowing for a more targeted and effective treatment approach.

In summary, our review underscores the significance of M2-TAM-Exos-ncRNAs in driving cancer cell resistance and reveals their potential as therapeutic targets. To advance this field, we recommend future research to focus on developing targeted therapies that specifically inhibit M2 TAMs and their exosome-mediated ncRNA transfer. Additionally, clinical studies should explore the feasibility and efficacy of these therapeutic strategies in overcoming drug resistance in cancer patients. By translating these findings into clinical practice, we have the potential to significantly improve treatment outcomes and extend the survival of patients with this devastating disease.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate Not applicable.

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