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Research progress on anti-ovarian cancer mechanism of miRNA regulating tumor microenvironment

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Ovarian cancer is the most deadly malignancy among women, but its complex pathogenesis is unknown. Most patients with ovarian cancer have a poor prognosis due to high recurrence rates and chemotherapy resistance as well as the lack of effective early diagnostic methods. The tumor microenvironment mainly includes extracellular matrix, CAFs, tumor angiogenesis and immune-associated cells. The interaction between tumor cells and TME plays a key role in tumorigenesis, progression, metastasis and treatment, affecting tumor progression. Therefore, it is significant to find new tumor biomarkers and therapeutic targets. MicroRNAs are non-coding RNAs that post-transcriptionally regulate the expression of target genes and affect a variety of biological processes. Studies have shown that miRNAs regulate tumor development by affecting TME. In this review, we summarize the mechanisms by which miRNAs affect ovarian cancer by regulating TME and highlight the key role of miRNAs in TME, which provides new targets and theoretical basis for ovarian cancer treatment.

KEYWORDS

miRNA, tumor microenvironment, ovarian cancer, exosomes, immunology

Abbreviations: microRNA, miRNA; tumor microenvironment, TME; scavenger receptor class B type 1, SCARB1; recombinant high-density lipoprotein-nanoparticles, rHDL NPs; α-smooth muscle actin, α-SMA; fibroblast activated protein, FAP; tumor-associated macrophages, TAMs; cancer-associated fibroblasts, CAFs; cell cycle protein-dependent kinase inhibitor 1B, CDKN1B; natural killer group 2 member D, NKG2D; natural killer, NK; Dendritic cells, DCs; Activin receptor-like kinase 7, ALK7.

Introduction

MicroRNAs (MiRNAs) are small non-coding RNAs that were first detected in Caenorhabditis elegans in early 1990, and since then studies have confirmed their presence in almost all species (1, 2). MiRNAs influence tumor and other disease processes by regulating post-transcriptional gene expression and participating in a variety of cellular activities (3, 4). MiRNAs are dysregulated in most tumors and the expression of specific miRNAs can characterize different tumors and stages (5, 6). Hence, miRNAs are used in the diagnosis, treatment and prognosis of cancer (7). The levels of cellular miRNAs change during tumor development, and recent studies have demonstrated that miRNAs can regulate tumor microenvironment (TME) to affect tumor angiogenesis (8, 9), immune invasion (10, 11) and tumor interstitial interactions (12, 13). TME is heterogeneous and contains a variety of cell types, including fibroblasts, endothelial cells, pericytes, immune cells, stromal stem and progenitor cells derived from local and bone marrow, and extracellular matrix (14, 15) (Figure 1). Some of them are altered during tumor development. Both tumor cells and their surrounding tissues influence cancer development, and TME is the main factor regulating both (16). As research progressed, the evolution of TME was found to complicate tumor formation, metastasis, and treatment (17).

Tumorigenesis, growth and metastasis are closely related to the internal and external environment in which tumor cells live, and tumor cells and their environment are both interdependent and competitive (18, 19). TME includes not only the structure, function and metabolism of tumor tissues, but also the intrinsic environment of tumor cells (20, 21). TME is complex and constantly evolving, including innate and adaptive immune cells in addition to stromal cells, fibroblasts and endothelial cells. Ovarian cancer is gynecologic cancer with high mortality rate (22), and due to the lack of characteristic clinical manifestations and effective diagnosis in the early stages, most patients have advanced disease and metastasis at the time of diagnosis. Ovarian cancer has a poor prognosis with a 5-year survival rate of approximately 47% (23). Previous studies have shown that the progression of ovarian cancer is not only associated with tumor cells but also with TME (24, 25). MiRNAs have been recognized as biomarkers for several human cancers, including ovarian cancer, and dysregulated miRNA expression is a prominent feature of ovarian cancer (26). Many studies have evaluated the expression profiles of miRNAs in tissue and serum samples from ovarian cancer patients in search of biomarkers (27–29). Several experiments have also demonstrated that miRNAs exert oncogenic or carcinogenic effects by degrading or inhibiting the translation of target mRNAs, such as miR-135a-3p (30), miR-200c (31), miR-216a (32)和miR-340 (33), these miRNAs regulate epithelial-mesenchymal transition and thus regulate the invasiveness of ovarian cancer cells. Recent studies have shown that the roles of miRNAs in TME include regulation of tumor angiogenesis (34, 35), tumor immune invasion (36, 37) and tumor interstitial interactions (12, 38), etc. (Table 1; Figure 2).

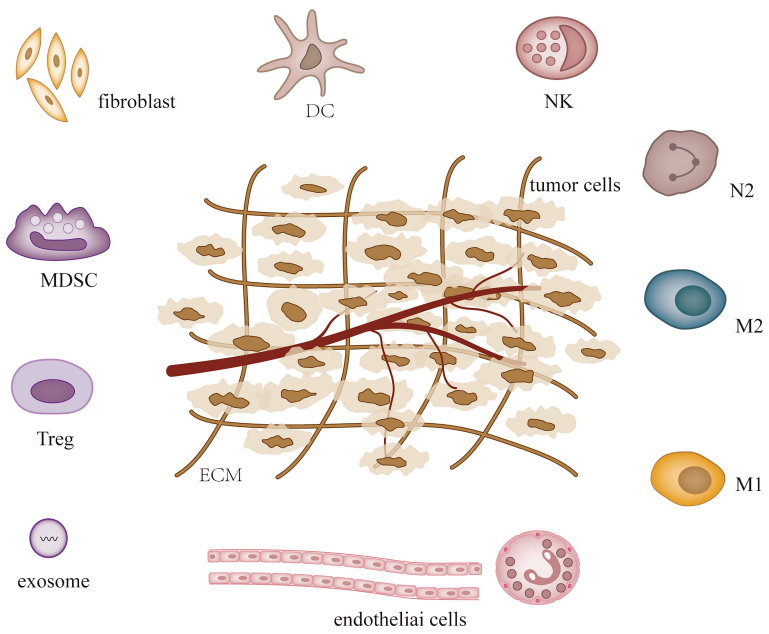

FIGURE 1
TME composition.

TABLE 1 Detailed information of miRNAs targeting TME to regulate ovarian cancer.

miRNA	Target genes	Related hallmark	Expression	reference
miR-204-5p	THBS1	Tumor angiogenesis	Promote	(10, 39)
miR-484 miR-642 miR-217	VEGFB/VEGFR2	Tumor angiogenesis	Promote	(40)
miR-21 miR-27a	HIF1- α/VEGF	Tumor angiogenesis	Promote	(41, 42)
miR-141-3p	JAK/STAT3/VEGFR2	Tumor angiogenesis	Promote	(43)
miR-205	PTEN/AKT	Tumor angiogenesis	Promote	(44)
miR-145	HIF1- α/VEGF	Tumor angiogenesis	Inhibit	(45)
miR-497	PI3K/AKT	Tumor angiogenesis	Inhibit	(46)
miR-195-5p	GSK3β/β-catenin	Tumor angiogenesis	Inhibit	(47)
miR-181	RTKN2	Tumor angiogenesis	Inhibit	(48)
miR-29b	MMP-2	Tumor-associated fibroblast	Inhibit	(49)
miR-214	CCL5	Tumor-associated fibroblast	Inhibit	(50)
miR-98-5p	CDKN1A	Tumor-associated fibroblast	Inhibit	(51)
miR-124	SPHK1	Tumor-associated fibroblast	Inhibit	(52)
miR-29a-3p miR-21-5p	STAT3	Immune-suppressive	Inhibit	(53)
miR-125b	ID8-VEGF	Immune-suppressive	Inhibit	(54)
miR-222-3P	SOCS3/STAT3	Immune-suppressive	Promote	(55)
miR-223	PTEN-PI3K/AKT	Immune-suppressive	Promote	(56)
miR-7	EGFR/AKT/ERK1/2	Immune-suppressive	Inhibit	(57)
miR-221-3p	CDKN1B	Immune-suppressive	Promote	(58)
miR-1246	Cav1/p-gp/M2	Immune-suppressive	Inhibit	(59)
miR-200b	KLF6	Immune-suppressive	Inhibit	(60)
miR-424(322)	PD-L1/PD-1 CD80/CTLA-4	Immune-suppressive	Promote	(61)
miR-142	Sirt1	Immune activity	Promote	(62)
miR-20a	MICA/B	Immune activity	Inhibit	(63)
miR-155	Ago2	Immune activity	Inhibit	(64)
miR-22	PI3K/AKT/MAPK	Immune activity	Inhibit	(65)
miR-503	Bcl2	Immune activity	Inhibit	(65)

In this review, we focus on the mechanisms by which miRNA-mediated regulation of TME affects the development of ovarian cancer.

MiRNAs regulate tumor angiogenesis in TME of ovarian cancer

Tumor angiogenesis is a hallmark of tumor growth, infiltration, and metastasis, and an increasing number of studies have shown its close association with TME (66, 67). Tumor growth and metastasis are dependent on the growth of blood vessels within the tumor, a process stimulated by soluble factors, of which vascular endothelial growth factor and its receptors are the main drivers (68). Recent *in vitro* and *in vivo* experiments have shown that miR-204-5p promotes ovarian tumor angiogenesis through THBS1 (39). By binding to scavenger receptor class B type 1 (SCARB1), recombinant high-density lipoprotein-nanoparticles (rHDL NPs) effectively deliver miR-204-5p inhibitors to tumors to inhibit tumor growth. This result provides new insights into miR-204-5p regulating tumor angiogenesis (39, 69). Angiogenesis plays a key role in the progression and peritoneal dissemination of ovarian cancer (70), and increased expression of VEGF has been found to promote the production of malignant ascites (71). Tumor samples from 198 ovarian cancer patients were analyzed by array and RT-PCR to confirm that three miRNAs (miR-484, miR-642 and miR-217) were able to predict chemotherapy resistance in ovarian cancer. This process is regulated by modulation of the tumor vascular system induced by the VEGFB and VEGFR2 pathways and is involved in tumor angiogenesis (40). MiR-21 and miR-27a induce ovarian cancer angiogenesis through upregulation of HIF1- α and VEGF (41, 42). Other pathways affected by miRNA

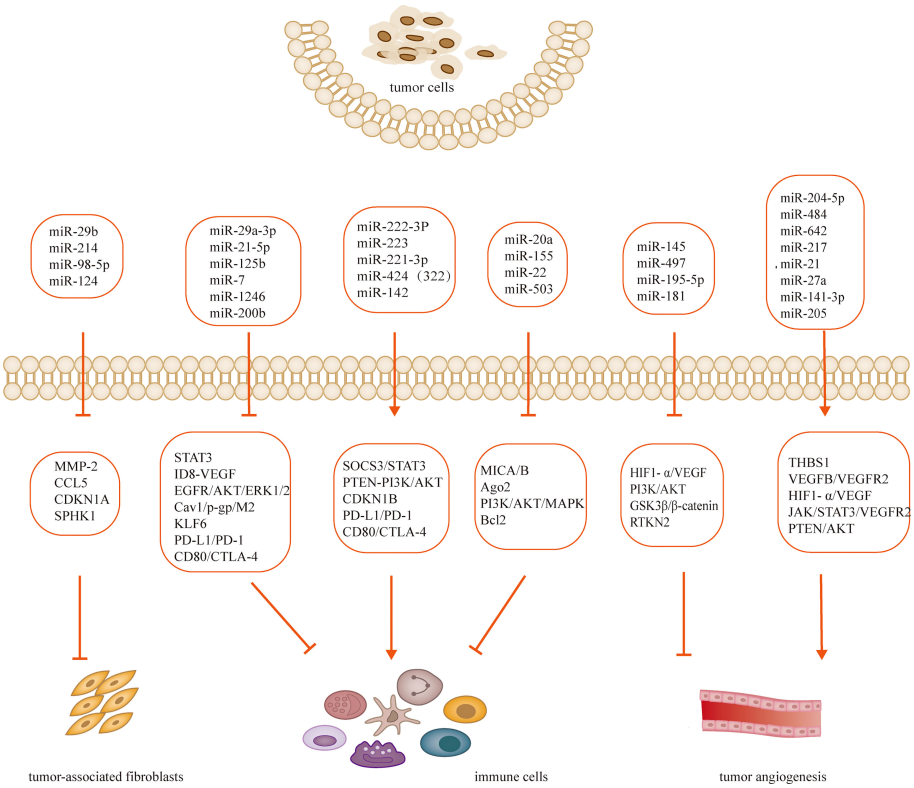

FIGURE 2
MiRNAs regulates TME and participates in the development of ovarian cancer.

dysregulation also contribute to angiogenesis in ovarian cancer. For example, miR-141-3p-containing extracellular vesicles from epithelial ovarian cancer cells promote vascular endothelial cell generation by activating the JAK/STAT3 signaling pathway and inducing VEGFR2 expression (43). Through different mechanisms, upregulation of miR-205 in ovarian cancer leads to increased angiogenesis through downregulation of the tumor suppressor PTEN and upregulation of the AKT signaling pathway (44). MiR-145 has tumor suppressive effects, and downregulation of miR-145 in ovarian cancer promotes angiogenesis through the upregulation of HIF-1 α and VEGF (45). MiR-497 targets vascular endothelial growth factor A through PI3K/AKT and MAPK/ERK pathways to inhibit ovarian cancer angiogenesis (46) Overexpression of microRNA-195-5p reduces cisplatin resistance and angiogenesis in ovarian cancer by inhibiting the psat1-dependent GSK3β/β-catenin signaling pathway (47). However, the role of aberrant regulation of miRNAs in ovarian cancer angiogenesis and development remains to be further investigated, which provides future therapeutic options and targets (72). Significant advances have been made in exploring the regulatory role of miRNAs in tumor angiogenesis. The rapidly increasing discoveries shall pave the way in the use of miRNAs as predictive biomarkers for anti-angiogenic treatments and as miRNA-based strategy against tumor angiogenesis in the future, though there are some challenges.

MiRNAs regulate CAFs in TME of ovarian cancer

Fibroblasts are the main cells in solid tumors and are stimulated to become cancer-associated fibroblasts (CAFs) by a variety of factors secreted by tumor cells or immune cells. Activated fibroblasts gain the ability to provide fertile soil for tumor progression (73, 74). CAFs are the major tumor mesenchymal component of TME (75), promoting tumor growth, angiogenesis, invasion and metastasis through extracellular matrix, chemokines, growth factors, cytokines, and stromal degrading enzymes, and mediating drug resistance (76). Studies have shown that CAFs influence the malignant progression, metastasis, drug resistance, and recurrence of ovarian cancer. After co-culture of SKOV-3 cancer cells with primary cultured human normal fibroblasts FP-96, the expression of the tumor suppressor miR-29b was downregulated, migration of SKOV-3 cells was increased, and

the activity of the miR-29b target MMP-2 was also increased (49). *In vitro* and *in vivo* experiments revealed that transient interference of three miRNAs, miR-31, miR-214 and miR-155, was sufficient to convert normal ovarian fibroblasts into induced CAFs, thereby promoting ovarian tumor growth and increasing the aggressiveness and migration of tumor cells. In contrast, the converse of this conclusion also holds, that by overexpressing downregulated miRNAs, CAFs can be reversed to more normal fibroblasts (77). Mitra et al. (50) identified one target of miR-214 as CCL5 and demonstrated that miR-214 inversely regulates CCL5. Importantly, downregulation of miR-214 increases the production of CCL5, leading to accelerated tumor growth. Anti-CCL5 antibodies blocked the effect of CAFs on tumor growth and migration. Cisplatin resistance is a common phenomenon in cancer treatment. CDKN1A was highly expressed in cisplatin-sensitive ovarian cancer cell lines, and silencing CDKN1A significantly promoted the proliferation and entry into the cell cycle of cisplatin-sensitive ovarian cancer cells and reduced apoptosis. MiR-98-5p is an exosomal miRNA derived from CAFs and promotes cisplatin resistance in ovarian cancer cells by targeting CDKN1A to inhibit CDKN1A expression (51). After miR-124 downregulation, normal fibroblasts exhibited tumor-associated fibroblast characteristics, including overexpression of α-smooth muscle actin (α-SMA) and fibroblast activated protein (FAP) and enhanced migratory and invasive abilities. Overexpression of miR-124 in CAFs reverses these features in normal fibroblasts (52). MicroRNA dysregulation is involved in the entire process of CAFs formation and executive function, and is closely related to the activation and formation of CAFs. These findings provide new insights into the communication between CAFs and cancer cells.

MiRNAs regulate immunosuppressive cells in TME of ovarian cancer

TME is composed of many non-tumor cells called stromal cells, including tumor-associated macrophages (TAMs) (78), CAFs (79), regulatory T cells (80), myeloid-derived suppressor cells (81), endothelial cells, pericytes, and platelets (82, 83). Macrophages are the main inflammatory cells (84) and when they are present in the TME, they are called TAMs (85). Over the past decade, convincing evidence has emerged for the tumor-promoting role of macrophages in TME (20, 86, 87). TAMs are transformed from macrophages affected by cytokines, growth factors and chemokines in TME and are classified as M1 and M2 types. The M1 type has antitumor effects, whereas the M2 type has a tumor-promoting effect (78, 88). TAMs are enriched in ovarian cancer tissues and ascites and affect ovarian carcinogenesis, metastasis and invasion *via* multiple mechanisms (89, 90). It was demonstrated that miR-29a-3p and miR-21-5p synergistically inhibit STAT3, regulate Treg/Th17 cells and induce an imbalance, creating an immunosuppressive microenvironment that promotes ovarian cancer progression and metastasis (53). Hyaluronic acid nanoparticles encapsulated with miR-125b specifically target TAMs in the peritoneal cavity of ID8-VEGF ovarian cancer mice and repolarize macrophages to an immune-activating phenotype (54). It was found that miR-222-3p is enriched in epithelial ovarian cancer-derived exosomes, activates macrophage polarization toward TAMs of the M2 phenotype, and participates in the SOCS3/STAT3 pathway to promote cancer progression (55). Hypoxia triggers macrophage aggregation and induces macrophages to develop a tumor-associated macrophage-like phenotype. Exosomes released from hypoxic macrophages are enriched with miR-223, which promotes drug resistance in ovarian cancer cells *in vivo* and *in vitro via* the PTEN-PI3K/AKT pathway (56).

Ovarian cancer is prone to peritoneal metastases compared to other tumors in the abdominal cavity (91, 92). Therefore, the immune microenvironment in the peritoneum is crucial for the progression of ovarian cancer (93). Previous reports have shown that the main immune cells in the peritoneum are M2 macrophages, especially TAMs (94, 95). Microarray analysis of exosomes showed that miR-221-3p was abundant in M2 exosomes and directly inhibited cell cycle protein-dependent kinase inhibitor 1B (CDKN1B). Further, miR-221-3p promoted proliferation and G1/S transition in ovarian cancer cells (58). Cav1 is a direct target gene of miR-1246 and has been shown to be involved in exosome transfer along with multiple drug resistance genes. When ovarian cancer cells were co-cultured with macrophages, miR-1246 was able to transfer macrophages to the M2 type (59). It has been noted that miR-200b is highly expressed in plasma-derived exosomes of ovarian cancer patients and induces macrophage M2 polarization through inhibition of KLF6 expression, promoting proliferation and invasion of ovarian cancer cells (60). Accumulating literature points to the central role that many miRNAs play in the regulation of these mechanisms of macrophages-mediated immunosuppression. However, the area of research remains largely unexplored.

MiRNAs regulate immunoreactive cells in TME of ovarian cancer

T lymphocytes are mainly divided into two subsets, CD4+ T cells and CD8+ T cells (96), and the specific immune responses they mediate are an important part of anti-tumor cellular immunity and are closely related to tumor development and prognosis (97). It was found that infiltration of CD8+ T cells was associated with prolongation of survival in tumor patients, but the inherent low immunogenicity of tumor cells with TME

suppressed the immune activity of T lymphocytes, leading to a decrease in the anti-tumor capacity of T lymphocytes (98, 99) MiR-424 (322) regulates the PD-L1/PD-1 and CD80/CTLA-4 pathways in drug-resistant ovarian cancer (100), and restoration of its expression reverses the chemoresistance that accompanies PD-L1 immune checkpoint blockage (101). The synergistic effect of chemotherapy and immunotherapy is associated with the proliferation of functional cytotoxic CD8+ T cells and the suppression of bone marrow-derived suppressor cells and regulatory T cells (61). Chen et al. found that artesunate promoted apoptosis of ovarian cancer cells by promoting CD4 + T cell differentiation to Th1 through miR-142 downregulation of Sirt1 (62). It was found that miR-20a binds directly to the 3 -untranslated region of MICA/B mRNA, leading to its degradation and reducing its protein level at the plasma membrane. A reduction in membrane-bound MICA/B protein, a ligand for the natural killer group 2 member D (NKG2D) receptor found on natural killer (NK) cells, γδ+ T cells and CD8 + T cells, allows tumor cells to evade immune-mediated killing. *In vitro* and *in vivo* tumor models, antagonism of miR-20a enhanced NKG2D-mediated tumor cell killing (63).

Dendritic cells (DCs) are a specialized group of antigen-presenting cells that are the focus of initiating and regulating innate and adaptive immune responses. DCs are important in anti-tumor immunity by regulating TME, recruiting and activating anti-tumor T cells (102). An increase in the density of DCs within the TME was found to correlate with improved prognosis in cancer patients (103), yet ovarian cancer cells and TME evade immune control by impairing the activation, maturation, antigen presentation, differentiation, and recruitment of DCs (104). Min et al. demonstrated that miR-22 targets YWHAZ and blocks PI3K/Akt and MAPK signaling pathways, and miR-503 downregulates Bcl2 expression. The increased expression of miR-22 and miR-503 in tumor-associated DCs results in their reduced survival and lifespan. Thus, tumor-associated miRNAs can target a variety of intracellular signaling molecules and cause apoptosis of DCs in TME (65).

Exosome-derived miRNAs regulate TME of ovarian cancer

Exosomes are tiny vesicles 30-150 nm in diameter secreted by cells, which are rich in various components such as proteins, lipids and nucleic acids and are significant in cellular communication, immune response, angiogenesis and tumorigenesis (105). There are a large number of miRNAs in exosomes (106), and exosome-derived miRNAs influence cancer progression, and they mediate ovarian cancer growth, invasion, metastasis, angiogenesis, and drug resistance through regulation of TME. Therefore, they are of great value in the early diagnosis and determination of prognosis of ovarian cancer (106, 107) (Table 2; Figure 3). MiRNAs play a role in communication

TABLE 2 Details of exosome-derived miRNAs targeting the TME to regulate ovarian cancer.

miRNA	Target genes	Related hallmark	Expression	reference
miR-940	CD163/CD206	Proliferation/Migtation	Promote	(108)
miR-124-3p	BAX/CASP9/CASP3	Proliferation	Inhibit	(109)
miR-205	VEGFA	Proliferation/Migtation	Promote	(110)
miR-6126	Integrin-β1	Proliferation	Inhibit	(111)
miR-940	SRC	Proliferation	Inhibit	(112)
miR-200	CD63/CD9	Migtation	Promote	(113)
miR-99a-5p	HPMCs	Migtation	Promote	(114)
miR-574-3p miR-30a-5p miR-922	CUL2	Enhance chemosensitivity	Inhibit	(115)
miR-183-5p	MECP2	Proliferation	Inhibit	(115)
miR-162	TEAD3	Enhance chemosensitivity	Inhibit	(115)
miR-146a	PI3K/AKT	Enhance chemosensitivity	Inhibit	(116)
miR-451	ABCB1	Enhance chemosensitivity	Promote	(117)
miR-186	ABCB1	Enhance chemosensitivity	Promote	(118)
miR-770-5p	ERCC2	Enhance chemosensitivity	Promote	(119)
miR-376c	ALK7	Enhance chemosensitivity	Promote	(120)
miR-130a miR-374a	MDR1/PTEN	Enhance chemosensitivity	Promote	(121)
miR-489	AKT3	Enhance chemosensitivity	Promote	(122)
miR-134	NF-κB1/c-Rel/ELK1	Enhance chemosensitivity	Inhibit	(123)

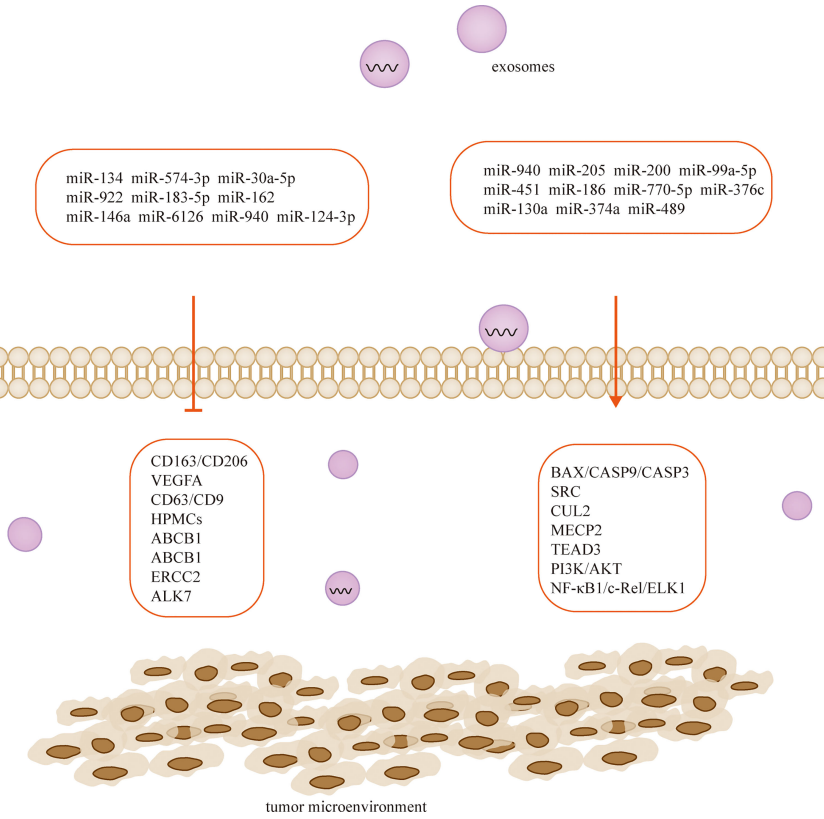

FIGURE 3
Exosome-derived miRNAs regulate TME and participate in the development of ovarian cancer.

between tumor cells and TME through exosome secretion and transfer (107, 124). Meanwhile, exosomal miRNA expression is dysregulated in ovarian cancer, which reflects the malignant character of the tumor to some extent (125).

Cancer-derived exosomal miRNAs are considered to be mediators between cancer cells and TME (126, 127). In the context of proliferation, ovarian cancer cells release exosomal miR-205 that promotes cell proliferation and invasion by targeting vascular endothelial growth factor A (128). In contrast, the widely released exosomal miR-6126 (129) and miR-940 (110) from drug-resistant and sensitive ovarian cancer cells inhibited tumor growth by targeting integrin-β1 and proto-oncogene tyrosine-protein kinase (SRC), respectively. On the other hand, non-ovarian cancer-derived exosomes also inhibit the proliferation of ovarian cancer cells (111). For example, human adipocyte-derived exosomes have inhibitory effects on two ovarian cancer cells, A2780 and SKOV-3, by blocking the cell cycle and activating the mitochondria-mediated apoptotic signaling pathway, capable of inhibiting their proliferation and wound repair (112). MiR-205 is involved in the proliferation, migration, invasion and apoptosis of ovarian cancer cells by regulating the target gene VEGFA. Transient introduction of miR-205 mimics into SKOV3 cell-derived exosomes resulted in enhanced ovarian cancer cell proliferation, migration and invasion, attenuated ovarian cancer cell apoptosis, downregulation of epithelial-mesenchymal transition protein E-cadherin, and elevated Vimentin (128). The let-7 family miRNA transcripts were found in both ovarian cancer cell lines and their exosomes and were more abundant in OVCAR-3 cells than in SKOV-3 cells. The let-7 and miR-200 families in exosomes are associated with the aggressiveness of ovarian cancer cells (130). Exosomal miR-99a-5p in the serum of ovarian cancer patients promotes invasion by increasing the expression of fibronectin and vitreous junction protein in adjacent peritoneal mesothelial cells (109). Studies have confirmed that miR-940 is highly expressed in exosomes isolated from ascites of ovarian cancer patients. Furthermore, miR-940 stimulated M2 phenotypic polarization, which in turn promoted proliferation and migration of ovarian cancer (113).

Chemotherapy is the mainstay of cancer treatment, but some patients develop chemotherapy resistance, with ovarian cancer

having the highest recurrence rate associated with drug resistance, this phenomenon significantly limits the long-term outcomes of cancer patients, resulting in 5-year survival rates as low as 30%. Cellular resistance develops through long treatment cycles or intrinsic pathways. CDKN1A was highly expressed in cisplatin-sensitive ovarian cancer cell lines, and silencing CDKN1A significantly promoted the proliferation and entry into the cell cycle of cisplatin-sensitive ovarian cancer cells and reduced apoptosis. The cancer-associated fibroblast-derived exosome miR-98-5p increases ovarian cancer cell proliferation and promotes cisplatin resistance by targeting CDKN1A (51). Microarray data downloaded from the Gene Expression Omnibus database revealed that miR-574-3p, miR-30a-5p and miR-922 may mediate the HIF 1 cancer signaling pathway through regulation of CUL2, and miR-183-5p may affect cell proliferation through regulation of MECP2. Downregulation of miR-162 may promote TEAD3 expression through the Hippo signaling pathway, and this miRNA is associated with poor prognosis. Through experimental validation, researchers predicted that these genes may be potential therapeutic strategies for ovarian cancer (114). Similarly, exosomal miR-146a derived from human umbilical cord MSCs increased the sensitivity of SKOV3 ovarian cancer cells to docetaxel and paclitaxel *via* the LAMC2-mediated PI3K/Akt axis (108). Human ovarian cancer cell lines OVCAR3, A2780, A2780/DDP and A2780/Taxol were exposed to paclitaxel or cisplatin transfected with or without miR-186, and miR-186 was found to induce sensitivity of ovarian cancer cells to paclitaxel and cisplatin by targeting ABCB1. This finding demonstrates for the first time that miR-186 increases the sensitivity of ovarian cancer cells to paclitaxel and cisplatin by targeting ABCB1 and regulating the expression of GST-π (115). MiR-770-5p was significantly reduced in cisplatin-resistant patients, and it acts as an anti-oncogene that increases chemosensitivity in ovarian cancer patients by downregulating ERCC2. Thus miR-770-5p may be a useful biomarker for predicting sensitivity to cisplatin chemotherapy in ovarian cancer patients (116, 118). Activin receptor-like kinase 7 (ALK7) and its ligand Nodal induce apoptosis in human epithelial ovarian cancer cells. Ye et al. examined the regulation of ALK7 by miRNA and demonstrated that miR-376c was able to target ALK7. Overexpression of miR-376c blocked cisplatin-induced cell death, while anti-miR-376c enhanced the effect of cisplatin (119).

Discussion

The past research that suggested that cancer develops only from changes in tumor cells has been replaced by the fact that the cellular microenvironment plays a key role in these processes. Therefore, new studies are needed to better explain the relationship between tumor cells and other cells that make up TME. Tumorigenesis and progression have causes in the tumor cells themselves as well as in TME. In recent years, miRNAs have been extensively studied, either as biomarkers or to demonstrate their potential to inhibit cellular processes. Because of this, miRNAs have great potential for the development of new cancer therapies. It was found that miRNAs are widely involved in various biological processes, including their regulatory roles in ovarian cancer progression. Several studies have demonstrated the involvement of miRNAs in the interaction between TME and ovarian cancer cells. The specific mechanisms of miRNAs are still being explored, but some miRNAs have been considered as biomarkers of tumors and have become therapeutic targets. For example, miR-204-5p, miR-484 and miR-21 promote ovarian cancer progression by regulating tumor angiogenesis in TME; miR-29b and miR-214 inhibit ovarian cancer progression by regulating CAFs; miR-125b, miR-1246 and miR-221-3p are able to inhibit/promote ovarian cancer progression by regulating immunosuppression and immunoreactive cells. These miRNAs serve as regulatory factors not only as clinical biomarkers, but also as potential therapeutic targets. It has been widely recognized that exosomes are rich in miRNAs and that exosomal miRNAs are significant in TME as signaling molecules for intercellular communication. Tumor cells transmit exosomal miRNA to cancer cells or normal cells, and conversely, fibroblasts, macrophages, etc. can also deliver exosomes to cancer cells. Exploring the role of miRNAs in TME can contribute to the search for biomarkers and probe the pathogenesis of tumors. Although many advances have been made in this area, many problems are still faced. More clinical data are needed to support the application of miRNAs as biomarkers for clinical diagnosis and detection, as well as to develop appropriate formulations for clinical treatment.

In summary, we have highlighted recent advances in the understanding of tumor microenvironmental interactions mediated by miRNAs. This article summarizes several miRNAs target important cancer cell–regulatory molecules and are involved in a complex network of signaling between cancer cells and the tumor microenvironment. In addition to their involvement in direct cell-to-cell signaling, several miRNAs are secreted through microvesicles or exosomes and affect cancer cell growth and metastasis. Some of the current challenges in miRNAs therapeutics involve selecting the right target and optimizing the delivery systems. Advances in miRNAs therapeutics have enabled us to target miRNAs alterations in a highly specific and robust manner in preclinical models. Nevertheless, studies of miRNAs-mediated interactions, specifically those focused on understanding the origin of miRNAs alterations, are needed to improve targeted therapy.

Author contributions

All authors reviewed the literature, wrote the paper, and agree to be accountable for the work's content. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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