CANCER
COMMUNICATIONS
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EMT-associated microRNAs and their roles in cancer stemness and drug resistance

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Abstract
Epithelial-to-mesenchymal transition (EMT) is implicated in a wide array of malignant behaviors of cancers, including proliferation, invasion, and metastasis. Most notably, previou studies have indicated that both cancer stem-like properties and drug resistance were associated with EMT. Furthermore, microRNAs (miRNAs) play a pivotal role in the regulation of EMT phenotype, as a result, some miRNAs impact cancer stemness and drug resistance. Therefore, understanding the relationship between EMT-associated miRNAs and cancer stemness/drug resistance is beneficial to both basic research and clinical treatment. In this review, we preliminarily looked into the various roles that the EMT-associated miRNAs play in the stem-like nature of malignant cells. Then, we reviewed the interaction between EMT-associated miRNAs and the drug-resistant complex signaling pathways of multiple cancers including lung cancer, gastric cancer, gynecologic cancer, breast cancer, liver cancer, colorectal cancer, pancreatic cancer, esophageal cancer, and nasopharyngeal cancer. We finally discussed the relationship between EMT, cancer stemness, and drug resistance, as

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Abbreviations: 5-FU, fluorouracil; ADGRE2, adhesion G protein-coupled receptor E2; BOK, Bcl2 related ovarian killer; Cathepsin L, CTSL; CAVIN2, caveolae-associated protein 2; CRC, colorectal cancer; CSC, cancer stem cell; CTSB, cathepsin B; DEDD, death effector domain-containing; DOX, doxorubicin; E2F2, E2F transcriptional factor 2; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal-transition; EOC, epithelial ovarian cancer; ERRFI1, ERBB receptor feedback inhibitor 1; ESCRT, endosomal sorting complex that is required for transport; EZH2, enhancer of zeste homolog 2; FAK, focal adhesion kinase; FOXO1, forkhead box protein O1; FOXQ1, forkhead box Q1; FZD7, frizzled class receptor 7; GAS5, growth arrest-specific 5; GATA3, GATA binding protein 3; GBM, glioblastoma multiforme; GDPD5, glycerophosphodiester phosphodiesterase domain containing 5; Gli1, GLI family zinc finger 1; GSK-3β, glycogen synthase kinase 3β; HCC, hepatocellular carcinoma; ITGB3, integrin β3; IL-6, interleukin 6; IL6R, interleukin 6 receptor; LAD, lung adenocarcinoma; MCRS1, microspherule protein 1; MCTS1, malignant T-cell amplified sequence 1; MET, mesenchymal-epithelial transition; miRNA, microRNA; MMP-2, matrix metalloproteinase-2; MMP-9, matrix metalloproteinase-9; NFATC1, nuclear factor of activated T-cells 1; NRP1, neuropilin-1; NSCLC, non-small-cell lung carcinoma; OC, ovarian cancer; ORF, open reading frames; PC, pancreatic cancer; PIK3CD, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta; PEBP1, phosphatidylethanolamine binding protein 1; PEBP4, phosphatidylethanolamine binding protein 4; PTP1B, protein-tyrosine phosphatase 1B; RBICC1, RB1-induced coiled-coil 1; RKIP, Raf kinase inhibitor protein; SALL4, sal-like protein 4; SCLC, small cell lung cancer; SMAD2, SMAD family member 2; SMAD4, SMAD family member 4; SOCS3, suppressor of cytokine signaling 3; STAT3, signal transducer and activator of transcription-3; TDGF1, teratocarcinoma-derived growth factor 1; TKI, tyrosine kinase inhibitor; TMZ, temozolomide; TP53INP1, tumor protein p53 inducible nuclear protein 1; UBE2C, ubiquitin-conjugating enzyme E2 C; VEGFA, Vascular endothelial growth factor A; VitD, Vitamin D; ZEB1, zinc finger E-box binding homeobox 1

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well as looked forward to the potential applications of miRNA therapy for malignant tumors.

KEYWORDS

cancer, epithelial-to-mesenchymal transition, microRNA, cancer stem cell, cancer stemness, drug resistance

1 | INTRODUCTION

The epithelial-mesenchymal-transition (EMT) represents a morphogenetic process that is associated with the invasiveness [1], metastasis [2], and chemoresistance [3] of malignant tumors. In cancer cells undergoing EMT, the expression of mesenchymal markers, including N-cadherin [4] and vimentin [5], is up-regulated and the expression of the epithelial markers, including E-cadherin [4] and ZO-1 [6], was down-regulated. Moreover, the essential program of EMT depends on EMT-associated transcriptional factors, such as zinc finger E-box binding homeobox (ZEB1 and ZEB2), zinc finger proteins (Snail and Slug), and Twist-family of basic helix-loop-helix (bHLH) transcription factors (Twist1, Twist2, and inhibitors of DNA binding and cell differentiation) [7, 8].

MicroRNAs (miRNAs) are a group of non-coding single-stranded small RNAs (18-22 nucleotides) that suppress gene expression by binding to the 3'-UTR of target mRNA [9–11]. Mounting evidence exhibited that miRNAs play a crucial role in the malignant behaviors of cancer cells, including EMT-related cancer metastasis [12]. Therefore, a better understanding of the roles of EMT-associated miRNAs can help us further explore their potential diagnostic, prognostic, and therapeutic values [13].

2 | EMT-ASSOCIATED miRNAs IN CANCER STEM CELLS (CSCs)

CSCs, a special range of cancer cells, are capable of unlimited self-renewal and differentiation, thereby contributing to the initiation, progression, metastasis, and development of drug resistance of malignant tumors [14–16]. Over the past decade, a lingering issue regarding CSCs is how to identify and select them. Nowadays, CD44 [17] and CD133 [18] have been the two most common surface markers used to characterize CSCs. In addition, aldehyde dehydrogenase is also a critical biomarker of CSCs due to their ability to self-renew [19]. Recently, CD73 was found to be correlated with the features of CSC since it elevated the expression of Sox9 in dual ATK-mediated signaling pathways via regulating the expression of *c-Myc*, and down-regulated glycogen synthase kinase 3β (GSK-3β). CD73 and Sox9 in

combination could more precisely predict the prognosis of tumor, suggesting that CD73 might serve as a marker of CSCs [20]. Several major factors (i.e. Nanog, Sox2, Oct4, KLF4, c-Myc) are essential for the maintenance of the pluripotency of CSCs, and they are regulated by miRNAs [21–23]. It was reported that EMT was intimately associated with to CSCs. EMT is a gradually adjusted process[24]. Cancer cells undergoing a partial EMT (hybrid epithelial/mesenchymal phenotype) acquire stem-like features [25]. This epithelial/mesenchymal hybrid status is crucial for tumor initiation, in which the Wnt signaling pathway plays a key part [26]. Apart from the Wnt signaling, there are other crosstalks between EMT and CSCs, such as the Notch/Jagged [27] and hedgehog [28] signal pathway. Most EMT transcriptional factors, which are modulated by a number of miRNAs, are implicated in CSCs, indicating that miRNAs can affect EMT-associated elements and subsequently exert an impact on the stem-like properties of CSCs [29, 30].

2.1 | EMT-associated miRNAs that inhibit cancer stemness

miR-99a prevents EMT progression and reduces CSC population, both *in vitro* and *in vivo*, by directly suppressing the expression of E2F transcriptional factor 2 (*E2F2*) and adhesion G protein-coupled receptor E2 (*ADGRE2*) [29]. Zhou *et al.* [31] illustrated that miR-125b overexpression could attenuate EMT phenotype and CSC generation by inhibiting SMAD family member 2 and 4 (*SMAD2* and *SMAD4*). miR-145 targets multiple stem cell transcription factors, and the action was found inversely correlated with EMT in colorectal cancer (CRC). Furthermore, Snail could elicit resistance to radiotherapy by repressing the expression of miR-145 [32]. miR-199a-5p conferred its tumor-suppressing function in triple-negative breast cancer by inhibiting EMT and stemness by down-regulating its potential target phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta (*PIK3CD*) [33]. Loss of miR-205 was found to expand mammary stem cell populations, enhance self-renewal, and promote EMT. Jagged1 secreted by the tumor stroma significantly suppressed miR-205 [34]. Moreover, the loss of miR-205 induced cell

stemness by activating NOTCH2 suggests that there might be a jagged1/miR-205/NOTCH2 signaling pathway that regulates cancer stemness [34, 35]. In prostate cancer, miR-218 suppressed the exhibition of CSC-like properties and EMT by binding to its potential target GLI family zinc finger 1 (*Gli1*) [36]. Vascular endothelial growth factor A (VEGFA) upregulated Sox2, resulting in cancer cell invasion, self-renewal, and metastasis triggered by Slug overexpression plus miR-452 loss [37]. miR-504, which is involved in the Wnt-β-catenin pathway, was shown to suppress malignant behaviors of glioblastoma multiforme (GBM), including aggression, migration, EMT, and stemness by directly inhibiting frizzled class receptor 7 (FZD7) [38]. miRNA sponges with multiple tandem miRNA binding sites could separate miRNAs from their target mRNAs [39]. In CRC, hypoxia upregulated the expression of a newly-identified lncRNA AK000053 in a HIF-1α-dependent manner, and functioned as a miR-508 sponge. Additionally, loss of miR-508 resulted in the overexpression of zinc finger E-box binding homeobox 1 (*ZEB1*), *Bmi1*, and sal-like protein 4 (*SALL4*), subsequently leading to EMT and cancer stemness, and poor survival of CRC patients [40]. The downregulation of miR-1247 induced by cancer-associated fibroblasts boosted the performance of EMT and escalated cell invasion and stemness. In addition, neuropilin-1 (*NRP1*) served not only as the miR-1247 target but also as a coreceptor of EGFR signaling [41]. Han *et al.* [42] illustrated that miR-4319 repressed cell proliferation, EMT, and cancer stemness by targeting forkhead box Q1 (*FOXQ1*) at the post-transcriptional level in hepatocellular carcinoma (HCC).

miR-203 was found to be not only a stemness-suppressing factor but also an anti-apoptotic factor and was downregulated by the EMT-associated transcriptional factor, *ZEB1* [43]. In renal cell carcinoma, miR-203 inhibited LncRNA HOTAIR and induced a tumor-suppressor effect, i.e., suppressing EMT via the PTEN/PI3K/ATK pathway, which was involved in a recognized lipid kinase dubbed Acylglycerol kinase [44].and the progress was also decrease the expression of KLF4 and Nanog[44, 45]. miR-203 inhibited the migration, endothelial cell tube formation, and stemness of prostate cancer cells, with Slug being downregulated. Moreover, miR-203, by targeting Slug, further repressed the GSK-3β/β-catenin signaling pathway [46]. Besides, silencing miR-203 enhanced the stemness of colon cancer cells, with several EMT activators up-regulated, in which Snail could inhibit miR-203 expression. Additionally, hyaluronan and CD44 suppressed miR-203 expression via activating c-Src kinase [47].

Canonical tumor suppressor miRNAs, such as miR-34a, miR-200 family, and let-7, interact in various signaling pathways involving inhibition of CSCs and EMT. In ovar-ian cancer, let-7a, miR-200c, and miR-186 could significantly reverse resistin-induced EMT and stemness [48]. Dong *et al.* [49] reported that miR-34a and miR-137 directly targeted Snail, thus suppressing EMT and sphere-forming capability of ovarian cancer cells, and leading to more favorable survival outcome of the patients. In high grade serous ovarian cancer cells with Snail knockdown, let-7 expression was up-regulated, and Nanog and Lin28 were down-regulated, suggesting that Snail/Let-7 axis might be an intersection between stemness and EMT [50]. miR-204, miR-200c, and miR-34a inhibited cancer stemness and EMT, leading to self-renewal and metastasis of breast cancer [14]. EMT and CSC properties were involved in the lung cancer risk of PM2.5, and chronic PM2.5 could significantly downregulate the levels of three stemness-associated microRNAs, Let-7a, miR-16 and miR-34a [51]. Weng *et al.* [52] identified an oncogene called malignant T-cell amplified sequence 1 (*MCTS1*), which mediated cancer stemness and EMT in triple-negative breast cancer by up-regulating interleukin 6 (IL-6) expression, elevating interleukin 6 receptor (IL6R) level and increasing the population of tumor-promoting M2 macrophages. Nonetheless, miR-34a could reverse the carcinogenic effect of MCTS1 by inhibiting IL-6R expression and triggering M1 polarization. ZNF281 not only interacted with Nanog, OCT4, Sox2, and c-Myc, but also induced cancer stemness markers LGR5 and CD33 in CRC. The expression of ZNF281 was up-regulated by Snail but down-regulated by tumor suppressor miR-34a [53]. And miR-200c and miR-141could regulate the expression of Bmi1 and ZEB1 in HCC with bile duct tumor thrombus [54]. The inflammation-induced transcription factor, that is a nuclear factor of activated T-cells 1 (*NFATC1*) functioned as a paramount regulator of cell plasticity in pancreatic cancer[55]. Particularly, *NFATC1* drove EMT to reprogram and bestowed pancreatic cancer cells with the phenotype that CSCs possessed via Sox2-dependent transcription of EMT and stemness factors, which was antagonized by antithetical p53-miR200c signaling [55].

Together, it is demonstrated that EMT and stemness share the similar signal pathways, which are mediated by miRNAs. EMT-associated miRNAs could inhibit the stemness features in various cancer types due to suppressing the specific gene and the downstream signal pathways.

2.2 | EMT-associated miRNAs that promote cancer stemness

miR-10b promoted CSC features, such as stemness and self-renewal. It is regulated by TWIST and TGF-β, and they are both associated with CSCs [56–58]. Moreover, miR-10b indirectly affected stem markers OCT4 and SNAIL

expression in breast cancer through the PTEN/PI3K/AKT pathway [58]. In breast cancer, the up-regulation of TGF-β-induced miR-10b-5p contributed to tumor-related myoepithelial cells acquiring invasiveness phenotype and CSCs occurring through targeting RB1-induced coiled-coil 1 (*RBICC1*) [57]. Thus, miR-10b is a bona fide regulator of the clonal potential and migration capability of CSCs. Hypoxic microenvironment-induced miR-210 up-regulation, in breast cancer stem cells, inhibited E-cadherin by binding to its open reading frames (ORF) and inducing the over-expression of its transcription repressor Snail [59]. miR-577 is involved in the metastasis of TGF-β-induced gastric cancer by targeting caveolae-associated protein 2 (*CAVIN2*). In addition, TGF-β activated miR-577 via the NF-κB signaling pathway [60]. In normal human colonic epithelial cells, an elevated expression of miR-1207-5p could reinforce stemness of the cancer cells as demonstrated by significantly enhanced morphological phenotype of EMT and increased levels of mesenchymal and CSC markers [61]. miR-5188 targeted forkhead box protein O1 (*FOXO1*) and reduced the nuclear translocation of β-catenin directly, it could promote the activation of Wnt signaling to downstream EMT, cancer stemness, and c-Jun both in HCC and breast cancer. In addition, c-Jun activated miR-5188 expression at the transcriptional level, forming a positive feedback loop, which could be induced by hepatitis X protein in HCC [62, 63].

Though the majority of EMT-associated miRNAs inhibit the stemness, there still exsit some EMT-associated miRNAs promiting the cancer stemness, which is mentioned above. For the most cases, these miRNAs facilitate the stemness properties by blocking related tumor-suppressive signals.

3 | EMT-ASSOCIATED miRNAs INVOLVED IN THE DEVELOPMENT OF DRUG RESISTANCE OF CANCER

Long-term drug therapy tends to result in drug resistance of cancer, a tough challenge facing clinicians. The development of drug resistance is multifactorial and EMT is a key factor [64]. Moreover, several miRNAs co-regulate EMT and drug resistance. Therefore, understanding the function of relevant miRNAs and the pathways involved will help us gain insight into and eventually sort out the problem.

3.1 | Lung cancer

In docetaxel-resistant lung adenocarcinoma (LAD), over-expression of miR-26a could suppress cellular pro-liferation, increase apoptosis rate and switch EMT to mesenchymal-epithelial transition (MET), both *in vitro* and *in vivo*, by downregulating the enhancer of zeste homolog 2 (EZH2) that was reported to induce EMT via binding to the PTEN promoter to a certain extent [65, 66]. Down-regulated miR-130a was associated with multidrug resistance in various cancers [67–69]. Moreover, miR-130a reportedly targeted MET and enhanced TRAIL-sensitivity in non-small-cell lung carcinoma (NSCLC) cells [70]. miR-146b targets protein-tyrosine phosphatase 1B (*PTP1B*), and miR-218 directly targets Slug/ZEB2 signaling pathway, as well as let-7c suppresses ABCC2-transporter and Bcl-xl were all shown to be capable of reversing EMT, thereby lowering the resistance of lung cancer cells to cisplatin [69,71,72]. Overexpression of teratocarcinoma-derived growth factor 1 (*TDGF1*), an epidermal growth factor (EGF)-related gene, generated a phenotype of erlotinib resistance, both in epidermal growth factor receptor (EGFR)-mutated and EGFR-tyrosine kinase inhibitor (TKI)-sensitive NSCLC cells, which was confirmed by *in-vitro* studies, in murine xenograft models and clinical patients. Mechanistically, SRC and ZEB1 activated by TDGF1 stimulate EMT by down-regulating miR-205. As a consequence, up-regulated miR-205 might repress SRC and ZEB1 activation in a TDGF1-dependent fashion, restoring the sensitivity to erlotinib. Furthermore, targeting both EGFR and SRC might overcome inherent EGFR-inhibitor resistance in EGFR-mutated NSCLC patients positive for TDGF1 [73]. When PRKCA was directly targeted to repress FAK/Ras/c-Myc signaling pathway, miR-296-3p stimulated its own expression, forming a feedback loop that blocked cisplatin chemoresistance and EMT signaling [74]. Additionally, miR-296-3p was inactivated by DDX5/HDGF/β-catenin signaling, leading to a more aggressive metastasis and stronger chemoresistance in lung adenocarcinoma (LAD) [74]. It was also reported that silencing c-Myc regulated by miR-451-induced MET in docetaxel-resistant LAD cells through decreasing the expression level of matrix metalloproteinase-2 (MMP-2), matrix metalloproteinase-9 (MMP-9), Snail, p-ERK as well as p-GSK-3β and increasing E-cadherin expression. Furthermore, patients with high miR-451 expression had significantly)$P < 0.05$(more favorable prognosis compared with those with low miR-451 expression. These findings suggested that miR-451/c-Myc/ERK/GSK-3β axis played a crucial role in suppressing EMT phenotype in docetaxel-resistant LAD [75]. Yue *et al*. [76] reported that miR-483-3p reversed EMT to MET and inhibited the invasion, migration, and metastasis of lung cancer cells resistant to gefitinib. In molecular terms, miR-483-3p directly targeted integrin β3 (*ITGB3*), and thereby inhibited downstream focal adhesion kinase (*FAK*)/*ERK* signaling pathways. Moreover, the miR-483-3p deficiency in gefitinib-resistant

lung cancer cells might be ascribed to the hypermethylation of its own promoter. It was reported that miR-495 served as an oncogenic miRNA or a tumor-suppressor in a variety of cancers [77–79]. Intriguingly, different theories are proposed about its function in NSCLC and small cell lung cancer (SCLC). In NSCLC, miR-495 decreased vimentin but increased E-cadherin at both transcriptional and translational levels [80]. Additionally, miR-495 reversed cisplatin resistance by suppressing drug resistance genes ERCC1 and ABCG2 in cisplatin-resistant NSCLC cells [80].Of note, ubiquitin-conjugating enzyme E2 C (UBE2C), which promotes EMT, was found to mediate miR-495 in the reversal of cisplatin resistance [80].Furthermore, the combination of siUBE2C and cisplatin caused the in vitro down-regulation of vimentin and up-regulation of E-cadherin in mRNA and protein levels. miR-495 was also found able to inhibit tumor growth in vivo. These results indicated that the miR-495-UBE2C-ERCC1/ABCG2 axis could restore the sensitivity to cisplatin by down-regulating anti-drug genes and inhibiting EMT in cisplatin-resistant NSCLC [80]. However, miR-495 promoted the EMT-related chemoresistance of SCLC via ETK/BMX. This study provided a promising strategy of restoring the sensitivity of SCLC to multiple drugs, including doxorubicin, cisplatin, and VP-16 in SCLC: i.e., by expressing miR-495 or depleting ETK/BMX [79].

Canonically, the miR-200 family, consisting of miR-141, miR-200a, miR-200b, miR-200c, and miR-429, serves as tumor suppressors in assorted cancer types, including lung cancer. It is well-known that miR-200 participates in the TGF-β-induced EMT. Typically, the inhibitory effect of miRNA depends on the number of binding sites in the 3'UTR of the target mRNA. Burk et al. [81] found that TGF-β2 was a direct target of miR-200. However, Gregory et al. [82] reported that miR-200 worked on all the three TGF-β isoforms, indicating that miR-200 influences the expression of TGF-β in both direct and indirect manners due to the lack of binding sites in TGF-β1 and TGF-β3. Besides, the prolonged exposure to TGF-β significantly inhibited the level of miR-200 because there were more methylated cytosine phosphate guanine)CpG) in the miR-200 promoter. By up-regulating miR-200b and miR-141, and down-regulating ZEB1 in NSCLC cells, nintedanib was capable of reversing TGF-β1-induced EMT and resistance to gefitinib. Thus, the combined use of gefitinib and nintedanib promises to be a new alternative for the treatment of NSCLC cells, since it takes care of both the resistance to gefitinib and EMT phenotype [83]. In TGF-β-mediated EMT, the miR-200 family depletion led to an up-regulated expression of ERBB receptor feedback inhibitor 1 (ERRFI1), a negative regulator of EGFR. The ERRFI1-mediated decrease of EGFR took place simultaneously with a TGF-β-induced EMT-related kinase switch of cancer cells to an EGFR-independent state with AKT activated.

In primary tumor xenografts of patient-derived lung and pancreatic cancers that carried wild-type EGFR, the tumor MIG6 (mRNA)/miR200 ratio was negatively associated with the responsiveness to erlotinib in vivo. This indicated that a low ratio of ERRFI1 to miR-200 might serve as a potential predictor of the tumor responsiveness to EGFR-TKIs [84]. In addition to the TGF-β signaling, miR-200c might be related to the obstruction of paclitaxel resistance in lung cancer cells via cathepsin L (CTSL)-mediated EMT. Moreover, miRNA-200c and CTSL were mutually attached in a feedback loop [85]. Interestingly, Krentz Gober et al. [86] indicated that the signal containing miR-140/141/200c was probably regulated by the cell cycle instead of TGF-β. Particularly, this study revealed that the inhibition of TGF-β did not suppress EMT in lung cancer cells but induced an EMT-intermediate state, which overturns the traditional notion about TGF-β-mediated EMT. Proliferation/growth signals by constitutively-activated EGFR might depend on TGF-β and, in this context; there might be an interaction between TGF-β and EGFR signaling pathways that obstruct EMT progression instead of stimulating it. This assumption needs to be further verified with more researches, preferably involving cellular or tumoral field.

Researchers have failed to reach a consensus about the function of miR-155 either. On the one hand, conspicuous discrepancies were observed in the expression levels of miR-155 and miR-200c, which were dramatically decreased in gefitinib-resistant NSCLC cells. Apart from this finding, the expression of SMAD2 and ZEB1 were identified as the target of miR-155 and miR-200c, respectively, were substantially up-regulated. As expected, the E-cadherin expression was down-regulated upon restrictive histone modification, whereas vimentin was up-regulated after active histone modification. Besides, this deficiency of miR-155 and miR-200c might be correlated with the epigenetic modifications-induced EMT and might promote the loss of sensitivity to gefitinib irrespective of the secondary EGFR mutation, which some gefitinib-resistant cells possess [87]. On the other hand, miR-155 was found to induce EMT by targeting RHOA at the post-transcriptional level [88]. Moreover, microspherule protein 1 (MCRS1) promotes TGF-β1-induced EMT and triggers resistance to cisplatin and cetuximab by up-regulating ABCB1 (a multidrug-resistance gene) at the transcriptional level. Nevertheless, MCRS1 was directly mediated by miR-129, indicating that miR-129 was a tumor suppressor that impacted cellular behaviors by regulating the expression of MCRS1 in NSCLC cells. To sum up, the miR-129/MCRS1/miR-155 signal axis offers a new perspective

for us to understand the molecular mechanism of EMT and drug resistance development, two events that are indicative of the invasion and metastasis of tumor [89]. More researches are warranted to understand the diversified role of miR-155.

Several miRNAs also play oncogenic parts in lung cancer. The miR-134/487b/655 cluster located on chromosome 14q32 was also found to cause the TGF-β1-induced EMT and influence the gefitinib resistance by directly repressing MAGI2 and its repression subsequently led to the depletion of PTEN in lung cancer. EMT was related to the loss of drug sensitivity and acquisition of resistance to EGFR-TKIs, whereas preservation of an epithelial phenotype ensured a favorable response to EGFR-TKIs even in LAD patients harboring wild-type EGFR genes [90–92]. These researches indicated that EMT was responsible for the resistance to EGFR-TKIs, independent of EGFR status. The miR-134/miR-487b/miR-655 cluster promises to be a therapeutic strategy for patients with advanced LAD in the case of EMT phenotype [93]. Upregulated miR-15b and miR-27a contributed to EMT and the resistance to cisplatin both *in vivo* and *in vitro* by targeting phosphatidylethanolamine binding protein 4 (*PEBP4*) and phosphatidylethanolamine binding protein 1 (*PEBP1/RKIP*), respectively [94, 95]. By modulating EMT, miR-21 reinforced the invasiveness and migrating ability of cisplatin- and paclitaxel-resistant LAD cells by targeting *HBP1* [96]. A noticeable shift was observed from the epithelial to the mesenchymal phenotype after the miR-127 level was elevated in lung cancer cells, and this shift was related to the increased resistance to the EGFR inhibitor and the tumor-propagating potential [97]. In cancer cells, up-regulated miR-127 led to an evident change from the epithelial to the mesenchymal phenotype, and this change was related to their stem-like features, enhanced resistance to the EGFR receptor inhibitor, and tumor-spreading potential. On the other hand, suppressing miR-127 could substantially reverse this malignant transition, impaired the stem-like traits and the *in vivo* tumorigenicity of malignant cells.

3.2 | Gastric cancer

The expression of miR-200c and ZEB2 was down- and up-regulated, respectively, in gastric cancer cells, with an evident decline of sensitivity to trastuzumab after treatment with TGF-β. Besides, miR-200c was able to restore the sensitivity to trastuzumab and repress the migration and invasion of cancer cells by inhibiting *ZEB1* and *ZEB2* [98]. miR-204 was inhibited in fluorouracil (5-FU)-resistant GC cells with the epithelial markers decreased and the mesenchymal markers increased simultaneously. In addition, restoration of TGFBR2, a target of miR-204, could recover resistance to 5-FU in GC cells with miR-204 upregulated [99]. Like miR-204, miR-574-3p could antagonize cisplatin resistance in gastric cancer by targeting *ZEB1* at both transcriptional and translational levels [100]. Nonetheless, the resistance to cisplatin or 5-FU in GC cells could be dramatically reduced by suppressing miR-17, which impaired EMT in GC cells via death effector domain-containing (*DEDD*) [101].

Therefore, different miRNAs are associated with antineoplastic drug in gastric cancer. More miRNAs are needed to explore to reduce the drug resistance in gastric cancer.

3.3 | Gynecologic cancer

Owing to the aberrant methylation engendered by DNMT1 over-expression, miR-30a-5p, and miR-30c-5p levels dropped significantly in cisplatin-resistant ovarian cancer (OC) cells. On the contrary, miR-30a/c-5p inhibited Snail and DNMT1 directly. Hence, a feedback loop between DNMT1 and miR-30a/c-5p could be a potential signature for addressing EMT and cisplatin resistance in OC, thereby providing a therapeutic strategy for epigenetically improving the responsiveness to anti-cancer agents [102].

Elevated miR-363 restored the sensitivity to cisplatin of cisplatin-resistant epithelial ovarian cancer (EOC) cells, both *in vitro* and *in vivo*. Moreover, studies showed that Snail, identified as a functional target of miR-363, was greatly elevated, not only in epithelial ovarian cancer(EOC) cell lines resistant to cisplatin but also in EOC patients. Moreover, the over-expression of Snail dramatically inhibited the repressing effect of miR-363 on cisplatin resistance of EOC cells, indicating that miR-363 modulates cisplatin resistance through Snail-induced EMT [96]. Zhang *et al.* [103] found that miR-1294 dysregulation affected OC cisplatin resistance by regulating IGF1R. IGF1R knockdown could suppress the proliferation, migration, invasion, and EMT of SKOVP/DDP cells. Further, elevated miR-1294 expression inhibited the development of resistance to cisplatin in OC. The miR-200 family also played a major role in the inhibition of EMT and sensitivity to carboplatin and paclitaxel of OC [104]. Besides, miR-200b and miR-200c were inhibited in taxane-resistant OC cells, and the inhibition was correlated with EMT progression as evidenced by the elevated expression level of MMP2, MMP9, and vimentin [105]. It was found that, in cervical cancer, miR-25-3p reversed EMT to MET with enhanced sensitivity to cisplatin in cisplatin-resistant cells by targeting *Sema4C* [106].

Knockdown of iASPP, a newly-identified key EMT inducer, sensitized cervical cancer cells to cisplatin and repressed cell proliferation *in vivo*. Moreover, iASPP promoted the expression of miR-20a targeting FBXL5 and BTG3 in a p53-dependent manner. miR-20a expression was increased and FBXL5 and BTG3 expression decreased in cervical cancer samples and the results were found to be related to a poor prognosis of the patients [64].

3.4 | Breast cancer

Enhanced miR-129-5p expression significantly increased E-cadherin and suppressed vimentin and N-cadherin expression in MCF-7/doxorubicin (DOX)-treated cells. EMT has been seen as an important mechanism responsible for the increased multidrug resistance in breast cancer [107, 108]. As expected, miR-129-5p substantially reduced IC50 of DOX, vincristine, and paclitaxel in the MCF-7/DOX-treated cells. However, the level of miR-129-5p in MCF-7 cells was lowered by EZH2 and SOX4, which act, respectively, as an epigenetic modification-silencing gene and a master control gene of EMT, respectively [109]. ZEB1 and ZNF217, identified as a transcriptional activator of TGF-β, were inhibited by miR-200c that could restore trastuzumab sensitivity and repress invasion and migration of breast cancer cells. Given that ZEB1 reportedly inhibited miR-200c, presumably, ZNF217 might participate in a feedback suppression of miR-200c through TGF-β/ZEB1 signaling [81].

Introducing miR-200c, inhibiting TGF-β signaling pathways, or silencing either ZEB1 or ZNF217 repressed the invasive capability and enhanced the sensitivity of breast cancer cells to trastuzumab. Therefore, the complicated interaction between miR-200c/ZNF217/TGF-β/ZEB1 and miR-200c/ZEB1 suppressed the metastasis and trastuzumab resistance of cancer cells, suggesting that EMT might be involved in the molecular induction of the malignant behaviors of breast cancers [110]. Recently, an lncRNA, termed Linck, was found to exaggerate the expression of ZEB1, and both were negatively related to the miR-200 family [111]. Due to the inhibitory capability of EMT, miR-708-3p was deemed as a tumor-suppressor miRNA in breast cancer. In addition, Lee *et al*. [112] suggested that reintroduction of miR-708-3p might be a promising therapeutic option for overcoming the chemoresistance of breast cancer cells and, at the same time, suppressing breast cancer metastasis.

miR-106b, miR-93, and miR-25 collectively form the miR-106b-25 cluster, and all target a transcriptional stimulator of E-cadherin, i.e., EP300. They were up-regulated in doxorubicin-resistant cells, with miR-25 playing the leading role in this phenotype. With this cluster, upregulation of a single miRNA would result in target cells obtaining the EMT phenotype, along with the proliferative ability upon treatment with doxorubicin [113].

EMT might be closely related to the malignant behaviors and increase multidrug resistance of breast cancers,while miRNAs could regulate the formation and development of EMT. miRNAs might be a promising therapeutic option for overcoming the chemoresistance of breast cancer cells.

3.5 | Liver cancer

In HCC, miR-125b could overcome the resistance to oxaliplatin through a mechanism involving the reduction of EVA1A-mediated autophagy, with a simultaneous loss of EMT phenotype [114]. Depletion of Smad4, a target of miR-130-3p, reversed EMT to MET in gemcitabine-resistant HCC cells. Furthermore, miR-130a-3p could restore the sensitivity to gemcitabine and inhibit cell growth in gemcitabine-resistant cells [115]. Vitamin D (VitD) has been deemed as a new regulator of the mTOR pathway [116]. Donatella *et al*. [117] demonstrated that, in a molecular network, VitD reduced oncogene expression and modulated EMT by up-regulating the expression of miR-375, and subsequently resulted in a reversal of the sensitivity to everolimus in everolimus-resistant HCC cell lines. Particularly, c-Myc was recently identified as a novel target of miR-375. The aforementioned results might provide a new approach to restore the sensitivity to mTOR inhibitor sensitivity in the treatment of HCC. The tumor-suppressing function of miR-612 was validated by inhibiting EMT and resistance to cisplatin and 5-FU through the PI3K/AKT2 signaling pathway. Recently, it could reportedly promote HCC metastasis via influencing the morphological formation of invadopodia and EMT. Studies showed that this phenomenon involved the HADHA-dependent lipid reprogramming [118, 119].

Nevertheless, miR-27a and miR-32-5p were highly expressed in liver cancer patients, particularly in cisplatin-resistant patients, predicting a poor prognosis. Further studies found that miR-27a regulated EMT partially by targeting the Raf kinase inhibitor protein (*RKIP*) and miR-32-5p triggered the activation of the PI3K/AKT pathway by inhibiting PTEN and generated exosome-mediated multidrug resistance by prompting EMT and angiogenesis [114, 120]. It has been known that Fbw7, which is regarded as a miR-233 target, suppressed EMT, and subsequently increased chemosensitivity of hepatocellular carcinoma cells [121–123]. Notch-1 has been confirmed to be one of the targets of FBW7 [124] and to induce EMT in human cancers [125]. Interestingly, genistein could promote the antitumor effect of miR-223 inhibitor by regulating EMT

and Notch-1 pathway [124]. Genistein in combination with miR-223 inhibitor can be a potential therapeutic strategy for the treatment of pancreatic cancer.

The production of EMT phenotype and the reversion from EMT to MET are related to tumor resistance. So in liver cancer, miRNAs could regulate EMT and improve the sensitivity of tumor drugs in liver cancer.

3.6 | CRC

miR-134 was reported to increase the sensitivity of CRC to oxaliplatin. However, it was found that astragaloside IV could inhibit the EMT of CRC by promoting the expression of miR-134, which obviously down-regulated the CREB1 signaling pathway, and further restored the sensitivity to chemotherapeutic agents [126]. miR-139-5p and miR-195-5p significantly suppressed the metastasis potential and chemo-resistance of CRC through EMT by targeting *BCL2* and glycerophosphodiester phosphodiesterase domain containing 5 (*GDPD5*), respectively [127, 128]. miR-195-5p bound to its direct target Notch2 to repress IL-4 secretion modulated by GATA3, ultimately leading to the inhibition of M2-like tumor-associated macrophage polarization [129]. Low miR-145 expression was related to poor responsiveness of rectal cancer patients to neoadjuvant chemoradiation on the basis of 5-FU chemotherapy. Mechanistically, Slug repressed the activity of the miR-145 promoter in CRC cells. In addition, the ectopic expression of Slug lowered the sensitivity to 5-FU, and inversely, the reappearance of miR-145 dramatically increased 5-FU sensitivity *in vitro* [130].

By targeting adenomatous polyposis coli (APC), miR-125b, which is up-regulated by the CXCL12/CXCR4 axis, promotes the progression of EMT, thereby further activating the Wnt/β-catenin signaling pathway. Importantly, there existed a reciprocal positive feedback loop between miR-125b and CXCR4. Further *in-vitro* and *in-vivo* experiments on CRC verified a possible role of miR-125b, i.e., promoting EMT and autophagy, in the development of the resistance to 5-FU [131]. Intriguingly, although miR-514b-3p and miR-514b-5p are both derived from the same RNA hairpin, they each have different influence on the invasion and metastasis of CRC. miR-514b-3p inhibited migration and drug resistance of CRC cells by decreasing the expression of mesenchymal markers and increasing the expression of epithelial markers. On the contrary, miR-514b-3p played a pro-metastatic role by speeding up the process of EMT. However, the underlying mechanism remains unclear [40]. Apart from chemotherapeutic application, miRNAs can also regulate the effect of radiotherapy on CRC. For instance, miR-124 could enhance the sensitivity of CRC cells to radiation via inhibiting the expression of

a recently-identified EMT regulator and stemness inducer, PRRX1 [132].

3.7 | Pancreatic cancer

Hiramoto *et al.* [133] and Funamizu *et al.* [134] illustrated that miR-200b, miR-509-5p or miR-1243 overexpression could each increase the sensitivity to gemcitabine by suppressing EMT-associated gene expression, thereby upregulating the E-cadherin expression in pancreatic cancer. Moreover, over-expression of miR-125a-3p or miR-3656 played similar role by targeting *Fyn* and *RHOF*, respectively [128, 135]. However, TWIST1 overexpression attenuated the enhanced chemotherapeutic effects of miR-3656 [135]. On the locus of miR-203, the suppressive histone mark H3K27me3 was reduced by the loss of ZEB1. Mocetinostat, belonging to class I HDAC inhibitor, could affect drug resistance by down-regulating of ZEB1 expression and up-regulating miR-203. Remarkably, mocetinostat did not exert its effect of anti-resistance to gemcitabine on cancer cells, where ZEB1 had been low and miR-203 expression was high, suggesting that the effect of mocetinostat would diminish if miR-203 was already present and ZEB1 had not appeared. However, whether the effect of mocetinostat depends on miR-203 had not been proved since MTT activity was increased in gemcitabine-treated cells in either the presence or the absence of mocetinostat [43]. Epigenetic drugs for restoring chemo-sensitivity of cancers trapped in EMT phenotype, Short-time treatment of tumor cells with clinically-used nanomolar doses, without causing immediate cytotoxicity, could result in an antitumor "memory" reaction [136, 137].

On the contrary, miR-301 both regulated EMT and induced gemcitabine resistance by down-regulating E-cadherin expression [134]. An apoptosis-facilitating gene, dubbed Bcl2 related ovarian killer (BOK), was a target of miR-296-5p in PC cells. miR-296-5p mimic transfectants also had an aberrant expression of mesenchymal markers. In addition, these transfectants displayed an obviously low apoptosis ratio in reaction to gemcitabine and 5-FU, with the absence of BOK expression. These results suggested that miR-296-5p/BOK signaling axis did play a crucial part in the invasion, EMT, and drug resistance development in pancreatic ductal adenocarcinoma cells (PDAC) cells [138]. Growth arrest-specific 5 (GAS5), a lncRNA, was identified as a tumor suppressor due to its ability to inhibit the malignant behavior of various cancers [139]. Upregulated GAS5 repressed the stem cell-like features, EMT, and gemcitabine resistance of PC cells through directly binding the 3'UTR of miR-221 and subsequently enhancing the expression of its target, suppressor of cytokine signaling 3 (SOCS3) [140].

3.8 | Esophageal cancer

In esophageal squamous cell carcinoma, miR-125a-5p up-regulated the E-cadherin and down-regulated the N-cadherin and vimentin expression, with an enhanced cytotoxic effect of cisplatin, whose tumor-suppressive effects on patients were further confirmed by longer survival time and earlier tumor stage. Remarkably, signal transducer and activator of transcription-3 (STAT3) were targeted by miR-125a-5p. However, IL-6, which was extensively reported to activate the STAT3 signaling pathway, could block the tumor-repressing effect of miR-125a-5p [141, 142]. miR-221 promoted the resistance of esophageal adenocarcinoma to 5-FU, in part, by regulating Wnt/β-catenin-EMT pathways in a DKK2-dependent way [143]. There are few researches of EMT-associated miRNAs in esophageal cancer resistance and they are need to further explore.

3.9 | Nasopharyngeal cancer

After transfection with miR-139-5p mimics, the expression of mesenchymal markers, such as MMP-9 and Vimentin, was decreased while the expression of epithelial markers, such as ZEB1, β-cadherin, and E-cadherin, was upregulated in cisplatin-resistant NPC cells. These results exhibited that miR-139-5p might act as a tumor suppressor in the restoration of the sensitivity of NPC cells to cisplatin by regulating EMT [144]. miR-296-3p, which was negatively regulated by nicotine, inhibited PI3K/AKT/c-Myc or Ras/BRAF/ERK/MEK/c-Myc pathways to prompt its own expression in an MK2-dependent manner. Thus, the upregulation of miR-296-3p due to the feedback loop ultimately suppressed NPC cell metastasis and drug resistance partially via EMT. Besides, NPC patients with higher miR-296-3p expression had longer overall survival than those with lower miR-296-3p expression [145]. miR-205-5p facilitated the migration and invasion of cisplatin-resistant NPC cells by inhibiting PTEN expression, resulting in a decrease expression in E-cadherin and an increase expression in vimentin, N-cadherin, MMP-2, and MMP-9. These findings suggested that PTEN, deemed as a candidate target of miR-205-5p, exerted its tumor-repressive EMT-regulating function through the PI3K/AKT signaling pathway in NPC cells that acquire cisplatin-resistant phenotype [146]. In contrast, miR-374a inactivated pPI3K/pAKT/c-JUN network by directly targeting CCND1, inhibiting the downstream EMT-related genes and cell cycle progression. Intriguingly, this feedback loop was modulated by tumor suppressor PDCD4, which was further confirmed in clinical specimens [147]. However, it is possible that miR-374a

plays a complicated part in context-dependent carcinogenesis since it has been reported to serve as an oncogene in breast cancer progression. Nonetheless, its roles remain poorly understood in lung cancer pathogenesis [148–150]. The function of miR-374a needs to be further explored in various cancer types.

3.10 | Other cancers

miR-26b could reverse temozolomide resistance-mediated EMT in glioma by targeting Wee1 [151]. miR-140 plays a pivotal role in tumor-suppression for it protracted the survival of patients who had some tumors, including glioblastoma. Up-regulated miR-140-5p and down-regulated cathepsin B (CTSB) were strongly associated with enhanced temozolomide (TMZ) sensitivity in GBM. Knocking down CTSB inhibited mesenchymal transition. These results suggested that not only miR-140 targeted the CTSB signaling pathway, this signaling was also crucial in the inhibition of the innate resistance to TMZ [152]. Several studies suggested that miR-125a-3p was involved in the modulation of EMT and chemoresistance in prostate cancer cells [40, 147, 153]. In oral squamous cell carcinoma, it could promote EMT by upregulate PAK1 and occurred the resistance to cisplatin by upregulating YAP and ERCC1 protein Besides, miR-485-5p lowered the protein expression of PAK1 in OSCC cells. Contrary to the function of PAK1, miR-485-5p could reverse EMT and greatly obstructed the invasion and migration and sensitized cisplatin-resistant cells [154]. TGFβ-miR-499a-SHKBP1 axis orchestrated the EMT-related kinase switch that induced the resistance of CD166$^+$ osteosarcoma cancer cells to EGFR inhibitors, implying that the suppression of EMT-related kinase switch induced by TGFβ may reverse the chemoresistance to EGFR inhibitors [155]. Various miRNAs in drug resistance of different cancers are not clear entirely and they need further study in the future.

4 | EMT-ASSOCIATED miRNAs MEDIATE DRUG RESISTANCE BY THE DELIVERY OF EXOSOMES

Exosomes are a subgroup of extracellular vesicles and their diameter ranges from 40 nm to 160 nm [156]. Multiple studies have reported exosomes could mediate cellular communication under physiological and pathological conditions via transferring miRNAs [157]. Recently, exosomal miRNAs were found to play a pivotal role in EMT-mediated drug resistance. miRNAs can be loaded into exosomes by means of the endosomal sorting
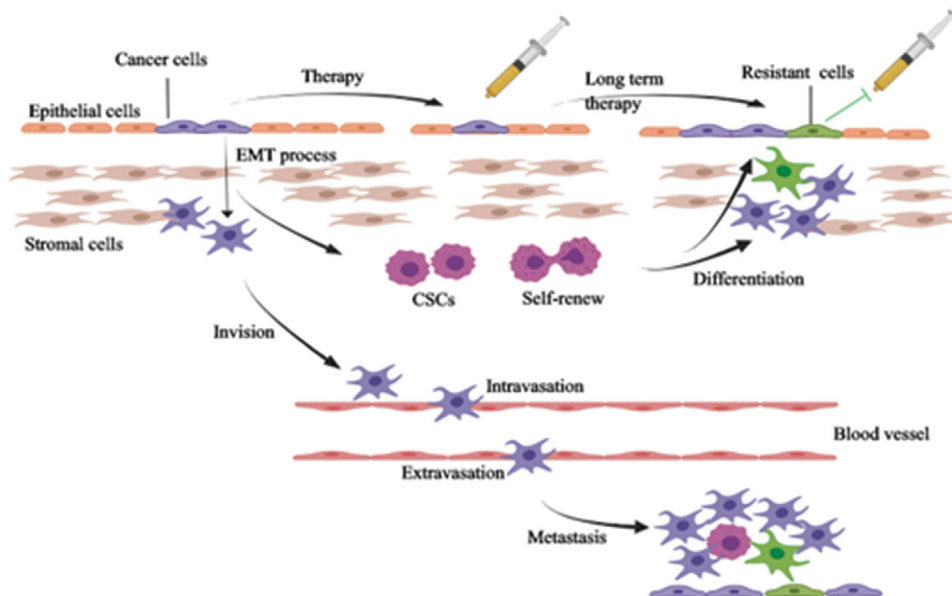
FIGURE 1 The relationship between EMT, stemness, and drug resistance. On one hand, the cancer cells harboring EMT phenotype may transform into drug-resistant cells after long-term therapy. On the other hand, the EMT may induce the generation of CSCs, which may go through a process of differentiation. Then the differentiated cells have the potential heterogeneity of being resistant to drug. Furthermore, EMT can generate the distant metastasis of cancer cells through the approaches of intravasation and extravasation

complex required for transport (ESCRT) [158]. Apart from the ESCRT-dependent manner, RNA-binding proteins could also recognize the specific motif in the 3′ portion of miRNA to facilitate its loading into exosomes [159]. Furthermore, ceramide might take part in the sorting of the bioactive molecules into exosomes and promoting domain-induced budding. The ceramide-rich domains curved spontaneously to form the invaginations, resulting in the generation of exosomes [160].

Exosomes containing miR-155 from paclitaxel-resistant gastric cancer cells were adequately absorbed by paclitaxel-sensitive GC cells, resulting in an exhibition of EMT and chemoresistance phenotypes. Mechanistically, miR-155 exerts its oncogenic effect by targeting tumor protein p53 inducible nuclear protein 1 (*TP53INP1*) and GATA binding protein 3 (*GATA3*) [161]. Besides, Santos JC et al. [162–164] demonstrated that exosome-mediated miR-155 was positively related to breast cancer cells with EMT-associated chemoresistance by mediating the depletion of C/EBP-β activity and targeting FOXO-3a-3′-UTR directly. However, the miR-128-3p could increase intracellular oxaliplatin accumulation, by suppressing the EMT pathway. Importantly, lower expression of miR-128-3p in patients with advanced CRC was associated with weaker responsiveness to oxaliplatin with poor prognosis. Moreover, after transfected into human normal colorectal epithelial cells, miR-128-3p was effectively parceled into secreted exosomes, which could be directly transferred to oxaliplatin-resistant cells, leading to an improvement in oxaliplatin

response. The possible mechanism might be that miR-128-3p suppressed oxaliplatin-induced EMT via inhibiting Bmi1 expression and decreased effluent oxaliplatin inside the cell through suppressing the expression of MRP5, a drug transporter [165].

According to the studies concerning EMT-associated exosomal miRNAs in drug resistance, some critical problems remain to be solved. For instance, how the exosomes target specific recipient cells is still unclear. Importantly, miRNAs can be loaded into exosomes for therapeutic use. miR-374a-5p and miR-214 inhibitors were incorporated into exosomes to reverse drug resistance by rescuing Neurod1 and PTEN in GC, respectively [166, 167]. However, the therapeutic effect and the potential side-effects should be further evaluated in large-sized clinical trials. More efforts have to be made to translate these research results into clinically effective therapies [168, 169].

5 | CONCLUSION AND FUTURE PERSPECTIVE

Given the nature of EMT, it is feasible to target the EMT to overcome the resistance. The therapeutic strategies can fall principally into three categories: (1) inhibiting the EMT initiation, (2) eliminating the cancer cells undergoing EMT, and (3) reversing the EMT to its opposite state, i.e., MET, since miRNAs play an important role in EMT-induced drug resistance. Targeting miRNAs might be a

TABLE 1 The target of EMT-associated miRNAs in different cancer types

miRNAs	Cancer types	Direct/indirect targets	Reference
Tumor suppresser miRNAs			
miR-25-3p	CC	Sema4C	[106]
miR-26a	LC	EZH2	[65]
miR-30a/c	OC	DNMT1	[102]
miR-34a	OC, LC, BC, CRC	Snail, MCTS1, ZNF281	[49, 51-53]
miR-99a	LC	E2F2, ADGRE2	[29]
miR-125b	HCC	Smad2, Samd4, EVA1A	[31, 114]
miR-125a-3p	PC, EC, PRC	Fyn, STAT3	[170, 141, 153]
miR-128-3p	CRC	Bmi1, MRP5	[165]
miR-129-5p	BC, LC	MCRS1	[89, 109]
miR-130a	LC, HCC	Smad4	[70, 115]
miR-134	CRC	CREB1	[126]
miR-137	OC	Snail	[49]
miR-139-5p	CRC, NPC	BCL2	[127, 144]
miR-140	LC, GBM	CTSB	[86, 152]
miR-145	CRC	Snail	[32]
miR-146b	LC	PTP1B	[71]
miR-155	LC,	Smad2	[87]
miR-195-5p	CRC	GDPD5, Notch2	[128, 129]
miR-199a-5p	BC	PIK3CD	[33]
miR-200 family	OC, HCC, LC, GC, BC, PC	NFATC1, CTSL, LIN28B, ERRFI1 ZEB1, ZEB2, ZNF17	[48, 54, 55, 85, 171, 172, 98, 81, 133]
miR-203	RCC, PRC, CRC, PC	PTEN, Slug, ZEB1	[43, 44, 46, 47]
miR-204	BC, GC	TGFBR2	[14, 99]
miR-205	BC, LC, NPC	Notch2, PTEN	[35, 73, 146]
miR-218	PRC	Gli1, Slug	[36, 71]
miR-221	EC	DKK2	[143]
miR-296-3p	LC, NPC	PRKCA, MK2	[74, 145]
miR-363	OC	Snail	[173]
miR-374a	NPC	CCND1	[147]
miR-375	HCC	c-Myc	[117]
miR-451	LC	c-Myc	[75]
miR-452	BC	Slug	[37]
miR-483-3p	LC	ITGB3	[76]
miR-485-5p	OSCC	PAK1	[154]
miR-495	LC	UBE2C	[80]
miR-499a	OS	SHKBP1	[155]
miR-504	GBM	FZD7	[38]
miR-508	CRC	ZEB1, Bmi1, SALL4	[98]
miR-574-3p	GC	ZEB1	[96]
miR-612	HCC	AKT2	[118]
miR-1247	PRC	NRP1	[41]
miR-1294	OC	IGF1R	[103]
miR-3656	PC	RHOF	[135]
miR-4319	HCC	FOXQ1	[42]
Let-7	OC, LC	ABCC2, Bcl-xl	[48, 51, 174]

(Continues)

TABLE 1 (Continued)

miRNAs	Cancer types	Direct/indirect targets	Reference
Oncogenic miRNAs			
miR-10b	BC	PTEN, RBICC1	[57, 58]
miR-15b	LC	PEBP4	[94]
miR-17	GC	DEDD	[101]
miR-20a	CC	FBXL5, BTG3	[64]
miR-21	LC	HBP1	[96]
miR-27a	LC, HCC	RKIP	[95, 175]
miR-32-5p	HCC	PTEN	[120]
miR-106b cluster	BC	EP300	[113]
miR-124	CRC	PRRX1	[132]
miR-134 cluster	LC	MAGI2	[93]
miR-155	LC, GC, BC	RHOA, GATA3, P53INP1, FOXO-3a	[88, 161, 164]
miR-196a	HCC	NA	[176]
miR-210	BC	E-cadherin, Snail	[59]
miR-221	PC	SOCS3	[140]
miR-233	HCC	Fbw7	[121]
miR-296-5p	PC	BOK	[138]
miR-495	LC	ETK	[79]
miR-577	GC	CAVIN2	[60]
miR-5188	HCC, BC	FOXO1	[62, 63]

Abbreviations: BC, breast cancer; CC, cervical cancer; CRC, colorectal cancer; EC, esophageal cancer, GC, gastric cancer; GBM, glioblastoma; HCC, Hepatic carcinoma; LC, lung cancer; PC, pancreatic cancer; PRC, prostate cancer; NPC, nasopharyngeal cancer; OC, ovarian cancer; OS, osteosarcoma; OSCC, oral squamous cell carcinoma; RCC, renal cell carcinoma.

promising approach in the treatment of cancer . In recent years, a great many studies intensively examined miRNAs and they have helped us better understand the role of miRNAs in the development, progression, and metastasis of tumors. Nonetheless, we still have a long way to go to fully elucidate the role of miRNAs in the development of drug resistance of tumor cells. In view of a large number researches of antitumor drugs, a database should be set up to cover the myriad information about drug targets and miRNAs, even the whole non-coding RNAs to provide support to researchers.In this review, we highlighted the pivotal part of miRNAs in EMT, cancer stemness, and drug resistance. The relationship among them is illustrated in Figure legends. Those EMT-associated miRNAs have showed complex functions in the regulation of cancer stemness and drug resistance phenotype: They bind to their targets and further impact the downstream pathways. (Table 1. The target of EMT-associated miRNAs in different cancer types) Even the same miRNA plays an opposite role in different cancer types.

Therefore, miRNAs can not only be used as potential diagnostic or prognostic markers but also are of therapeutic value. Targeting miRNAs to antagonize certain malignant properties of cancer may have more extensive clinical implications. The miRNA-based therapies are still confronted with some challenges, such as the off-target effect and lack of an optimal delivering system. The *in vivo* delivery of miRNAs remains a challenge due to their speedy excretion, incorrect intracellular release, poor biostability, endosomal escape, poor cellular ingestion, and immunogenicity. Thus, miRNA-based therapeutics will not be clinically available for cancer treatment until these problems are fully resolved.

DECLARATIONS

ETHICS APPROVAL AND CONSENT TO PARTICIPATE
Not applicable.

CONSENT FOR PUBLICATION
Not applicable.

AVAILABILITY OF DATA AND MATERIALS
Not applicable.

COMPETING INTERESTS
The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

S.Y. provided direction and guidance throughout the preparation of this manuscript. G.P. wrote and edited the manuscript. Y.L., L.S., and F.Z. reviewed and revised the manuscript. G.P. and F.Z. collected data. All authors read and approved the final manuscript.

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