MiRNA-mediated EMT and CSCs in cancer chemoresistance

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Abstract
Cancer stem cells (CSCs) are a small group of cancer cells, which contribute to tumorigenesis and cancer progression. Cancer cells undergoing epithelial-to-mesenchymal transition (EMT) acquire the chemoresistant ability, which is regarded as an important feature of CSCs. Thus, there emerges an opinion that the generation of CSCs is considered to be driven by EMT. In this complex process, microRNAs (miRNAs) are found to play a key role. In order to overcome the drug resistance, inhibiting EMT as well as CSCs phenotype seem feasible. Thereinto, regulating the EMT- or CSCs-associated miRNAs is a crucial approach. Herein, we conduct this review to elaborate on the complicated interplay between EMT and CSCs in cancer chemoresistance, which is modulated by miRNAs. In addition, we elucidate the therapeutic strategy to overcome drug resistance through targeting EMT and CSCs.

Keywords: miRNA, EMT, CSCs, Chemoresistance

Introduction
Cancer stem cells (CSCs) are a special subset of cancer cells, which have the ability to self-renew and contribute to tumor initiation, metastasis, and chemoresistance [1, 2]. So far, several surface markers of CSCs have been identified, such as CD24, CD44, CD133, and EpCAM, which facilitate the CSCs isolation and targeting [3, 4]. Importantly, aldehyde dehydrogenase (ALDH), ATP-binding cassette subfamily G member 2 (ABCG2), and c-kit have been additionally regarded as the CSC hallmarks, which contribute to chemoresistance by regulating drug metabolism or affecting the gene expression of drug efflux [5]. Recent studies have revealed that the generation of CSCs is likely driven by the epithelial-to-mesenchymal transition (EMT). EMT is a morphogenetic process, in which cancer cells lose their epithelial properties, such as the apical-basal polarity and cell junctions, while acquiring mesenchymal characteristics, including the increased capacity of migration and invasion [6]. Additionally, the activation of EMT confers the tumor cells with the capacity to resist various chemotherapeutics, which is also a crucial feature of CSCs [7].

MicroRNAs (miRNAs) are a part of non-coding single-stranded small RNAs (18–22 nucleotides) that can suppress gene expression through binding the 3' UTR of target mRNA [8]. With the further understanding of miRNAs, researchers find miRNAs can function as oncogenes or tumor suppressors to modulate tumor cell proliferation, apoptosis, immune response, and reshape microenvironment [9–12]. Recently, a growing number of studies report miRNAs play a pivotal role in regulating the EMT program and the CSCs genesis [13]. However, we still have few insights into the complicated relationship between cancer chemoresistance and miRNA-mediated CSCs and EMT. Therefore, we conduct this review to elaborate on the mechanistic link between CSCs as well as EMT, and summarize the role of EMT- or CSCs-associated miRNAs in cancer chemoresistance.

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**EMT program and CSCs**

Cancer cells undergoing the EMT process express more mesenchymal markers including N-cadherin as well as vimentin, and diminish the epithelial markers expressions like E-cadherin [14]. Loss of E-cadherin has been recognized to be related to cancer metastasis and the poor prognosis since nearly 20 years ago, then how to activate EMT draws considerable attention [15]. Numerous studies have reported the intricate EMT-associated signal pathways, in which the TGF-β-SMAD signal pathway has been well accepted [16]. Furthermore, Wnt signaling also contributes to the activation of EMT [17]. However, the complex signal pathways primarily activate a relatively small group of transcription factors to induce the EMT process. These transcription factors are termed as EMT-inducing transcription factors (EMT-TFs), which are typically categorized into three different protein families, including the ZEB (ZEB1 and ZEB2), Snail (SNAI1 and SNAI2, also termed as Snail and Slug), and basic helix–loop–helix (Twist1 and Twist2) families [18]. Notably, the EMT-TFs usually regulate the expression of one another and act together to activate EMT. For instance, Snail can increase the expression of Slug, Twist1, and ZEB1, which is regarded as an upstream regulator [19]. Due to the reciprocal interactions, it is difficult to determine the exact function of individual EMT-TF.

Apart from being modulated by specific signal pathways, EMT-TFs are also controlled by other regulators, especially miRNAs. MiRNAs affect the EMT process by directly or indirectly regulating specific EMT-TFs. The well-known examples are miR-200 and miR-34 families, which downregulates the expression of Snail and ZEB, respectively [20, 21]. Though the mechanism of the activation is becoming gradually clear, there remain some key problems to solve. For example, the experimental and clinical observations suggest the EMT program is reversible and dynamic, but how cancer cells harboring mesenchymal properties become epithelial again in the metastatic sites needs to be further explored.

CSCs are a small subpopulation of cancer cells with stem cell-like characteristics, including quiescence, self-renewal, and slow cell cycle. A growing number of studies indicate conventional chemotherapeutics mainly target the bulk non-CSCs population instead of the rare CSCs population that indeed cause the clinical relapse [22]. Mechanism explorations reveal that CSCs are resistant to chemotherapy owing to their quiescent state, increased drug efflux, and activate DNA repair [23]. When the chemotherapy ceases, CSCs that escape from cytotoxicity will revive from quiescence and promote tumorigenesis. Thus, eradicating CSCs are becoming a promising therapeutic approach to overcome chemoresistance and achieve clinical cure. Currently, the identification of these subpopulations primarily depends on the high expression of ALDH and surface markers like CD44 and CD133 [24]. However, it is still urgent to find other potent CSCs markers to select the patients who likely resist drugs in the clinic due to inter-patient variations and tumor heterogeneity [25]. This is critical to precisely targeting CSCs without impairing those stem cells from normal tissues.

**The relationship between EMT and CSCs**

Cancer cells undergoing EMT possess lots of stem-like traits, such as the elevated expression of CD44 and the increased capacity to form spheres [26]. These phenomena suggest EMT is closely related to the generation and maintenance of CSCs. Compelling evidence shows that CSCs may occur from progenitor cells or normal stem cells owing to the genetic and epigenetic mutations [27]. For instance, the overexpression of yes associated protein 1 (YAP1) that contributes to EMT can transform differentiated cancer cells into CSCs [28]. This characteristic example demonstrates that the abnormal expressions of EMT-related genes facilitate the generation of CSCs. CSCs live in a dynamic microenvironment, called niche, which is composed of stromal cells, immune cells, various cytokines and growth factors [29]. CSCs in such a niche are able to maintain their stemness state [30]. On one hand, the niche with hypoxia and high vascular intensity can directly maintain CSCs plasticity and survival [31]. On the other hand, the maintenance of CSCs can be reinforced by the EMT process under such a favorable microenvironment. For example, nestin is another CSCs marker that is upregulated by hypoxia-induced TGF-β-SMAD4 pathway activation [32]. Furthermore, cancer-associated fibroblasts and tumor-associated macrophages in the CSCs niche can secrete TGF-β to promote EMT, subsequently maintaining the CSCs features [33]. Additionally, CSCs have the potential to differentiate into non-CSCs. It is plausible that the aforementioned dynamic and reversibility of EMT can be partially attributed to the differentiation capacity of CSCs (Fig. 1).

The association between EMT and CSCs is supported by substantial experimental evidence concerning the mechanistic link. It is reported the activation of EMT and CSCs share similar signaling pathways, such as Wnt and Notch signals [34]. Notably, Scheel et al. found the autocrine of TGF-β and Wnt signal pathways of cancer cells were responsible for maintaining the EMT establishment and CSCs block. Blocking these autocrine signals could prevent cancer cells from acquiring CSCs properties even though the EMT program was activated [35]. Furthermore, Snail could facilitate the acquisition of dedifferentiated phenotype ultimately promoting the tumor-initiating capability by deacetylating active p53 [36]. Although substantial studies demonstrate the close relationship between EMT and
CSCs, whether the EMT program is necessary for driving the CSCs phenotype remains to be further explored. Having insight into this problem may help us make a therapeutic decision in targeting mesenchymal cells or only precisely eradicating the small subpopulation of CSCs in the future.

**MiRNA-mediated EMT and CSCs in chemotherapy resistance**

Though the studies about EMT focused on cancer metastasis at first, the link between EMT and cancer drug resistance has been increasingly recognized. Before the relation between EMT and CSCs was established, the mechanism of EMT-mediated drug resistance was unclear. In recent years, miRNAs as a hot topic have drawn considerable attention among numerous researchers. An increasing number of studies show miRNAs play a pivotal role in chemotherapy resistance, which is correlated to EMT or CSCs [37, 38]. Herein, we summarize the various roles of miRNAs in mediating EMT- or CSCs-associated chemoresistance (Fig. 2) (Table 1).

**Fig. 1** The connection between EMT and CSCs. CSCs can be generated by cancer cells that undergo a partial EMT process. Compared with cancer cells, CSCs are more invasive and drug-resistant and have great ability of tumor-initiation. CSCs are prone to intravasate into adjacent blood vessels. After entering the circulation, the metastatic CSCs will undergo transendothelial migration to extravasate into a new secondary site. Subsequently, CSCs can be transformed into cancer cells again via the MET process.

**MiRNAs facilitate EMT to induce chemotherapy resistance**

MiRNAs can contribute to chemoresistance by directly targeting the epithelial markers. For instance, miR-375 induces paclitaxel chemoresistance by directly suppressing E-cadherin in lung cancer [39]. Besides, miR-514b-5p can decrease the expression of E-cadherin to facilitate drug resistance. Intriguingly, despite derived from the identical RNA hairpin, miR-514b-3p plays an opposite role, which reverses the EMT-induced drug resistance [40]. However, how the precursor of miR-514 becomes the mature miR-514b-3p and miR-514b-5p with distinct roles remains to be further investigated. Furthermore, the miR-106b-25 cluster promotes doxorubicin resistance via repressing EP300, a transcriptional activator of E-cadherin [41].

There exist complex signal pathways of the EMT program, which miRNAs participate in. Wnt is a critical signal in regulating EMT-associated chemoresistance. Yu et al. reported miR-125b promoted the EMT process and induced 5-fluorouracil (5-FU) resistance in colorectal cancer through targeting the APC/Wnt/β-catenin...
pathway. Remarkably, the expression of miR-125b could be upregulated by CXCL12/CXCR4 [42]. In addition, miR-221 enhanced the resistant capacity to 5-FU of esophageal cancer via the Wnt/β-catenin pathway by directly targeting Dickkopf-2 [43]. PTEN, a tumor suppressor, is identified to participate in repressing EMT by inhibiting PI3K/AKT signal. Chu et al. found miR-93 contributed to eliciting EMT and facilitating doxorubicin resistance in breast cancer via the suppression of PTEN [44]. It was observed that miR-27a was dramatically upregulated in cisplatin-resistant lung adenocarcinoma. Mechanism exploration revealed that miR-27a targeted Raf kinase inhibitory protein to rescue Raf signal, which was involved in EMT-induced cisplatin resistance [45].

Exosomes are a subset of extracellular vesicles with a diameter ranging from 40nm to 160nm, which can mediate cell communication in physiological and pathological conditions via transferring specific cargos (nucleic acid or protein) [46]. Recently, it is reported that miRNAs carried by exosomes derived from drug-resistant cells can confer the resistant ability to drug-sensitive ones [47]. For example, CSCs and resistant cancer cells can secrete exosomal miR-155, which induces the EMT process to enhance the resistance to chemotherapy of breast cancer [48]. Besides, exosomal miR-155 was found to promote the EMT and chemoresistant phenotypes in gastric cancer by targeting GATA binding protein 3 and tumor protein p53-inducible nuclear protein 1 [49]. Fu et al. identified the transmission of multidrug resistance in hepatocellular carcinoma was attributed to exosomal miR-32-5p that inhibited PTEN/PI3K/AKT pathways [50]. On the other hand, exosomes can also regulate drug resistance by changing the transcriptome of cancer cells. Exosomes derived from mesenchymal-like prostate

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**Fig. 2** The mechanism by which some representative miRNA mediates EMT to affect chemotherapy resistance. MiRNA can regulate the EMT process by directly targeting the key proteins (E-cadherin and Vimentin) of EMT, modulating the expression of EMT-TFs (Snail, ZEB, and Twist), and influencing the EMT-associated signal pathways like Wnt, PTEN, TGF-β, and Ras signal. Furthermore, miRNA can be transferred by exosomes, which plays a key role in the EMT process. Cancer cells undergoing the EMT program exhibit the chemoresistant phenotype. In addition, the generation of chemoresistant CSC is partially attributed to the EMT.
Table 1: The role of miRNA-mediated EMT and CSCs in drug resistance

| miRNA     | Cancer type | Chemotherapy       | Role in chemosensitivity | Target                      | Ref.    |
|-----------|-------------|--------------------|--------------------------|-----------------------------|---------|
| miR-375   | CC          | Paclitaxel         | Decrease                 | E-cadherin [39]             |         |
| miR-514b-5p | CRC     | Cisplatin and irinotecan | Decrease                 | CDH1, CLDN1 [40]            |         |
| miR-514b-3p | CRC     | Cisplatin and irinotecan | Increase                 | FZD4, NTN1 [40]             |         |
| miR-125b  | CRC         | 5-FU               | Decrease                 | APC [42]                    |         |
| miR-221   | EC          | 5-FU               | Decrease                 | DKK2 [43]                   |         |
| miR-93    | BC          | Doxorubicin        | Decrease                 | PTEN [44]                   |         |
| miR-27a   | LC          | Cisplatin          | Decrease                 | RIKP [45]                   |         |
| miR-155   | BC          | Doxorubicin and paclitaxel | Decrease               | FOXO3a [48]                 |         |
| miR-32-5p | HCC         | S-FU               | Decrease                 | GATA3 and TP53 [49]         |         |
| miR-509-5p | PC       | Gemcitabine        | Increase                 | Vimentin [53]               |         |
| miR-138-5p | PC        | S-FU               | Increase                 | Vimentin [54]               |         |
| miR-30a   | PC          | Gemcitabine        | Increase                 | Snail [56]                  |         |
| miR-153   | PC          | Gemcitabine        | Increase                 | Snail [57]                  |         |
| miR-363   | OC          | Cisplatin          | Increase                 | Snail [58]                  |         |
| miR-34    | PC          | Gemcitabine        | Increase                 | Slug [59]                   |         |
| miR-27b   | LC          | Cisplatin          | Increase                 | Snail [60]                  |         |
| miR-27b, miR-34a | PC | Docetaxel | Increase                 | ZEB1 [61]                   |         |
| miR-181a  | TSCC        | Cisplatin          | Increase                 | Twist [63]                  |         |
| miR-186   | OC          | Cisplatin          | Increase                 | Twist [64]                  |         |
| miR-708-3p | BC        | Doxorubicin        | Increase                 | ZEB1 [66]                   |         |
| miR-218   | LC          | Cisplatin          | Increase                 | ZEB2, Slug [67]             |         |
| miR-200c  | LC          | Paclitaxel         | Increase                 | Cathepsin L [69]            |         |
| miR-200a  | BC          | Cisplatin          | Decrease                 | TPS3P1, YAP1 [72]           |         |
| miR-1243  | PC          | Gemcitabine        | Increase                 | SMAD4 [53]                  |         |
| miR-25-3p | CC          | Cisplatin          | Increase                 | Sema4C [74]                 |         |
| miR-31-3p | CC          | Cisplatin          | Increase                 | Sema4C [75]                 |         |
| miR-296-3p | NPC      | Cisplatin          | Increase                 | MK2 [77]                    |         |
| miR-1294  | OC          | Cisplatin          | Increase                 | PRKCA [78]                  |         |
| miR-128-3p | CRC       | Oxaliplatin        | Increase                 | Bmi1 and Mrp5 [83]          |         |
| miR-5100  | LC          | Cisplatin          | Decrease                 | Rab6 [84]                   |         |
| miR-125b  | BC          | Gemcitabine, Taxol | Decrease                 | BAK1 [86]                   |         |
| miR-455-3p | EC       | Cisplatin          | Decrease                 | NA [87]                     |         |
| miR-27b   | BC          | Docetaxel          | Increase                 | ENPP1 [89]                  |         |
| miR-328   | CRC         | 5-FU, HCPT         | Increase                 | ABCG2 [90]                  |         |
| miR-451   | CRC         | SN38               | Increase                 | ABCB1 [91]                  |         |
| miR-181b  | LC          | Cisplatin          | Increase                 | Notch2 [93]                 |         |
| miR-365   | HCC         | Cisplatin          | Increase                 | RAC1 [98]                   |         |
| miR-485   | LC          | Cisplatin          | Increase                 | CD44 [99]                   |         |
| miR-1246  | BC          | Docetaxel, epirubicin, gemcitabine | Decrease       | Cyclin G2 [100]             |         |
| miR-9-5p, miR-195-5p, miR-203a-3p | BC | Doxorubicin, Docetaxel | Decrease                 | ONECUT2 [101]               |         |
| miR-129-5p | BC        | Doxorubicin        | Increase                 | SOX4 [118]                  |         |
| miR-532-3p | CRC       | 5-FU, cisplatin    | Increase                 | ETS1 and TGM2 [119]         |         |
| miR-224   | CRC         | 5-FU               | Decrease                 | NA [124]                    |         |
| miR-145   | GBM         | TMZ, cisplatin     | Increase                 | Oct4 and Sox2 [127]         |         |

S-FU 5-fluorouracil, APC adenomatous polyposis col, ABCB1 ABC subfamily B member 1, ABCG2 ABC subfamily G member 2, Bcl1/BCL2 antagonist/killer 1, BC breast cancer, Bmi1 B lymphoma Mo-MLV insertion region 1 homolog, CC Cervical cancer, CDH1 Cadherin 1, CLDN1 Claudin 1, CRC colorectal cancer, EC esophageal cancer, ENPP1 adenosine triphosphatase/adenosine diphosphatase 5A, ETS1 V-Ets avian erythroblastosis virus E26 oncogene homolog 1, FOXO3a Forkhead O3, FZD4 frizzled family member 4.
cancer cells confer the recipient cells with the ability to resist enzalutamide, an androgen receptor antagonist. It was observed that the expressions of miR-21, miR-31, and miR-145 were upregulated with the activation of the TGF-β signaling pathway when the recipient cells took up the exosomes [51]. However, the content of exosomes hasn’t been identified. Although EMT-related pathways mediated by miRNAs in drug resistance have been broadly investigated, there remain several key problems about exosomal miRNAs-mediated drug resistance. For example, how the EMT-related miRNAs are loaded into exosomes hasn’t been exhaustively figured out. Furthermore, inhibition of drug resistance-induced exosomal miRNA cannot entirely abolish the resistance, indicating drug resistance is a complex process where other factors may be involved [52].

**MiRNAs inhibit EMT to overcome chemotherapy resistance**

There also exist numerous miRNAs that suppress chemoresistance by inhibiting the EMT process. To begin with, miRNA can inhibit mesenchymal markers like vimentin to overcome chemoresistance. Overexpression of miR-509-5p increases the sensitivity to gemcitabine in pancreatic cancer by targeting vimentin [53]. Furthermore, miR-138-5p that can be downregulated by TGF-β also targets vimentin to enhance the chemosensitivity to 5-FU in pancreatic cancer [54, 55].

Additionally, miRNAs can inhibit the EMT-TFs to overcome drug resistance. It was reported that miR-30a, miR-153, and miR-363 all targeted Snail to enhance chemotherapy sensitivity [56–58]. In addition, miR-34 and miR-27b were found to increase chemoresistance sensitivity through targeting Slug and Snail, respectively [59, 60]. Meanwhile, Zhang et al. identified miR-34a and miR-27b could enhance docetaxel sensitivity via inhibiting ZEB1 in prostate cancer [61]. Notably, hypoxia can repress the expression of miR-34a, attenuating its anti-tumor effect [62]. Thus, improving the hypoxic microenvironment will be a novel strategy to overcome the therapy resistance. Twist, another key EMT-TF, can be suppressed by miR-181a with the increased cisplatin sensitivity simultaneously [63]. Moreover, miR-185 was reported as a chemotherapy sensitizer through targeting Twist in not only ovarian cancer but also glioblastoma [64, 65]. As for ZEB, miR-708-3p acts as a ZEB1 suppressor to increase drug resistance in breast cancer [66]. Similarly, Shi et al. identified miR-218 served as a drug sensitizer through directly targeting ZEB2 in lung cancer, which provided a potential therapeutic strategy [67]. However, the therapeutic effect should be further evaluated because EMT-TFs often act cooperatively and are modulated by other upstream regulative EMT-TFs.

Through targeting the EMT-related signal pathways, miRNAs can exert their anti-chemoresistant functions. Generally, the miR-200 family, containing miR-141, miR-200a, miR-200b, miR-200c, and miR-429, serves as a tumor suppressor in manifold cancer types. It is well known that the miR-200 family decreases the expression of TGF-β to repress the EMT process and drug resistance [68]. In addition to the TGF-β/SMAD pathways, miR-200c can overcome chemoresistance by reducing Cathepsin I. that has been regarded as a potential target in cancer treatment [69, 70]. Moreover, the miR-200c/c-myc negative regulatory feedback loop is crucial for the EMT process and CSC properties as well as drug sensitivity [71]. Nevertheless, there exists an opposite voice about the role of miR-200. For instance, Yu et al. found miR-200a confer the sensitive breast cancer cells with the chemoresistant ability through antagonizing tumor protein p53-inducible nuclear protein 1 and YAP1 [72]. TGF-β signal is also regulated by other miRNAs. Recently, miR-1243 was found to increase the expression of E-cadherin and reverse drug resistance via suppressing SMAD4 [53]. Semaphorin 4C plays a key role in promoting TGF-β-induced EMT [73]. Overexpression of miR-25-3p and miR-31-3p can target Semaphorin 4C to reverse EMT in cisplatin-resistance cervical cancer cells [74, 75]. TGF-β can affect the expression of miRNAs in turn, to regulate the EMT, resulting in the change of drug sensitivity. For example, TGF-β can suppress miR-499a to induce drug resistance, which inhibits EMT in osteosarcoma through targeting SH3K binding protein 1 [76]. Furthermore, the Ras/Raf signal pathway has a significant influence on EMT and chemoresistance, too. It was found that miR-296-3p could suppress the expression of MAPK activated protein kinase 2 to inhibit the Ras/Braf/Erk/Mek/c-Myc pathway, ultimately reversing the chemoresistance in NPC [77]. In lung adenocarcinoma, miR-296-3p also contributes to the inhibition of Ras, leading to the increased chemotherapeutic sensitivity [78]. It is also reported that miR-296-5p inhibited stemness potency and EMT via BRM/SW12-related gene 1 and neuregulin 1, respectively [79]. Intriguingly, miR-95 knockdown could repress EMT and CSCs phenotype through dual
Drug resistance is the overexpression of the ATP-binding cassette (ABC) family, which transports drugs out of cells, protecting the cells from cytotoxicity [88]. MiRNAs can modulate the expression of the ABC family to affect the resistant phenotype in CSCs. For instance, miR-27b indirectly represses ABCG2 by affecting its localization on the cell surface. As a result, breast cancer patients with the downregulation of miR-27b was inclined to relapse due to the emergence of a small group of cells harboring CSCs properties [89]. In addition, miR-328 and miR-451 reverse the chemotherapy resistance by directly targeting ABCG2 and ABC subfamily B member 1 in CSCs, respectively [90, 91].

MiRNAs can regulate the stemness-associated signal pathways to overcome chemoresistance, in which the Notch signal plays a pivotal role [92]. Notch signal can contribute to the reduced sensitivity to cisplatin and the suppression of CSCs features while it is repressed by miR-181b in lung cancer [93]. Similarly, miR-136 enhances the antitumor effect of paclitaxel in ovarian cancer by decreasing Notch3 [94]. Another crucial pathway concerning the generation of CSCs is the Ras signaling pathway. Upregulation of miR-17-92 cluster can facilitate the exhaustion of pancreatic CSCs by reducing Ras and cyclin dependent kinase inhibitor 1 C, resulting in the reverse of chemoresistance [95]. Ras-related C3 botulinum toxin substrate 1 (RAC1) is also a subfamily of the Ras superfamily, which mediates intercellular adhesion, cell cycle, and epithelial differentiation [96]. Upregulation of miR-194 and miR-365 targeting RAC1 inhibits liver CSCs expansion, leading to the increased sensitivity to sorafenib and cisplatin [97, 98]. In addition to regulating the complicated signals, miRNAs are able to diminish the number of CSCs more directly—targeting the hallmarks of CSCs. For example, stemness features and CSC population were repressed by miR-485/CD44 axis in cisplatin-resistant lung cancer cells [99].

Exosome-loaded miRNAs are also vital to spread drug resistance to those sensitive cancer cells. Exosomal miR-1246 is related to stem-like traits and chemoresistance, which could serve as a prognostic predictor in breast cancer patients. Mechanically, miR-1246 exert its oncogenic role by inhibiting cyclin-G2 [100]. MiR-9-5p, miR-195-5p, and miR-203a-3p carried by exosomes all target One Cut Homeobox 2 (ONECUT2) to enhance the stemness of breast cancer. Notably, the upregulations of these exosomal miRNAs are induced by chemotherapy [101]. Additionally, gemcitabine-resistant pancreatic CSCs disseminate the resistant phenotype by delivering exosomal miR-210 [102]. Importantly, the upregulation of miR-210 is elicited by hypoxia [103], which indicates inhibiting exosomal miR-210 and improving the hypoxic microenvironment simultaneously may achieve a better therapeutic effect.
The therapeutic strategy of inhibiting EMT and CSCs to overcome chemoresistance

Since the roles of EMT and CSCs in chemoresistance are gradually determined, a promising therapeutic strategy for overcoming chemoresistance is to repress EMT and CSCs. The rapid progress of CSC-associated drug resistance is attributed to the advanced technique of identifying and isolating CSCs, which makes researchers analyze the distinct drug sensitivities between CSCs and non-CSCs. Nevertheless, the idea of precisely targeting CSCs is faced with several challenges. On one hand, the reliable hallmarks to accurately identify CSCs in bulk cancers are still insufficient. On the other hand, how to ensure the stem cells from normal tissues escape the cytotoxicity of chemotherapeutics remains to be solved. Fortunately, benefiting from the interplay between CSCs and the EMT program, a substituted therapy of targeting EMT seem feasible due to the existence of definite biomarkers and signal pathways.

Given that the EMT is dynamic and requires a certain process, the therapeutic approaches can be primarily divided into preventing EMT initiation, eliminating the cells undergoing EMT, and activating the opposite process of EMT—mesenchymal-epithelial transition (MET) [23].

TGF-β signal is among the best-characterized pathways in inducing EMT. Therefore, the blockade of the TGF-β pathway may be an effective approach in preventing the initiation of EMT and overcome drug resistance. As expected, several TGF-β inhibitors are undergoing clinical trials and achieve a certain therapeutic effect [104, 105]. However, TGF-β has a broad function in physiological and pathological conditions, which is not merely limited to affecting EMT. Hence, whether TGF-β inhibitors influence other biological processes need to be further evaluated. In addition, TGF-β serves as a tumor suppressor in early-stage cancer and it is cautious to choose the optimal medication time [106].

Another approach is to improve the tumor microenvironment, which also contributes to the activation of EMT. The conventional method is to inhibit tumor-associated inflammation and hypoxia. In recent years, with the gradual insight into the role of cancer-associated fibroblast and tumor-associated macrophage in EMT-associated metastasis, the strategy of targeting these cells has drawn considerable attention, especially targeting the exosomes derived from them [107, 108]. However, EMT triggered by these components of the tumor microenvironment remains under investigation.

As for eliminating the cells undergoing EMT, the initial attempt is to repress the EMT biomarkers. Kaschula et al. found ajoene derived from garlic could disrupt the vimentin filament network to exert the anti-metastatic function, while the role of overcoming drug resistance needs to be conducted [109]. However, the mesenchymal markers are also widely expressed in normal mesenchymal cells, leading to the potential off-tumor toxicities. Recently, Lou et al. reported the c-Src inhibitor could selectively target the overexpressed vimentin in triple-negative breast cancer, which may provide a new solution to this problem [110]. Another approach is to repress the specifically expressed gene in the EMT program. It was found that Axl was significantly upregulated during the process of EMT and knockdown of Axl by siRNA inhibited the metastasis and increased the overall survival in breast cancer [111]. In 2013, the first Axl inhibitor BGB324 entered clinical trials [112]. Recently, the recruitment of a phase II, multicenter clinical trial of BGB324 combined with pembrolizumab in treating triple negative breast cancer has been completed (NCT03184558).

From the perspective of the principle of EMT, reversing EMT to MET seems to be effective in overcoming drug resistance. It was reported the increased expression of intracellular second messenger cAMP induced MET via activating protein kinase A [113]. This study revealed a role of protein kinase A in maintaining and reinforcing the epithelial state, which suggested protein kinase A may act as a new therapeutic target. However, cancer metastasis is likely associated with the re-epithelization of mesenchymal cells or CSCs, which is aforementioned. Thus, choosing the proper time of this strategy needs to be particularly careful otherwise it may be a pro-metastatic factor.

Since the EMT is regulated by miRNAs, the exogenous introduction of miRNA mimics or antagonir may enhance the drug sensitivity. The downregulation of miR-129-5p and miR-532-3p are associated with the poor prognosis in manifold cancer types, which are involved in the EMT program [114–117]. Hence, Luan et al. and Gu et al. used miR-129-5p and miR-532-3p mimics, respectively, to enhance the chemosensitivity in vivo [118, 119]. Recently, miR-147, miR-335, miR-1976, and miR-4319 were identified as tumor suppressor miRNAs for inhibiting EMT and CSCs simultaneously [120–123]. However, their roles in reversing drug resistance have not been demonstrated clearly, which need to be further explored. On the contrary, miR-224 is responsible for the poor response of 5-FU, and silencing miR-224 by antagomir achieves the desired effect in colorectal cancer cells [124]. Nevertheless, miRNAs have broad functions due to their tissue specificity and target gene diversity. It remains unknown whether the inhibition of a specific miRNA will have an influence on other signal pathways. Moreover, the efficacy of RNA interference is likely to be reduced in vitro study due to the degradation and off-target effects.
Thus, it is important to select a proper delivery vehicle. Yang et al. used polyurethane-short branch polyethyleneimine as the vehicle to deliver miR-145 that can inhibit stem-like features and chemoresistance simultaneously [127]. However, the chemosynthetic carrier is faced with the challenge of biocompatibility in vitro.

Recently, delivering functional small RNAs by exosomes is a decent approach to solve these problems. Exosomes are stable and of biological origin, which can protect the cargos from being degraded [128]. Furthermore, the ligand/receptor on the exosome membrane is usually modified for better targetability. For instance, IL-3R is overexpressed on chronic myelogenous leukemia blasts [129], so Bellavia et al. coated a fragment of IL-3 on exosomes to precisely target CML cells. It has been shown the engineered exosomes carrying BCR-ABL siRNA can significantly inhibit cell growth [130]. However, the exosome-based delivering strategy is also faced with quite a few defects. It is urgent to develop techniques to realize the large-scale preparation of therapeutic exosomes. Besides, the therapeutic effect should be further verified in a large number of clinical studies.

**Conclusion**

In summary, the deep understanding of the link between the EMT program and the CSCs status provides us with new insight into therapy resistance. Cancer cells undergoing EMT acquire the CSCs properties, which are regulated by multiple factors, such as EMT-TFs and various signal pathways. In this process, miRNAs play a pivotal role. Importantly, targeting EMT and CSCs will be a promising therapeutic strategy in overcoming chemoresistance. Furthermore, inhibiting the EMT-induced miRNAs or introducing the EMT-suppressed miRNAs is also attractive. However, applying these therapeutic approaches to clinical practice remains a long way to go. More efforts should be put into identifying cancer type specific miRNAs and refining delivery approaches for miRNAs into cancer cells.

**Abbreviations**

5-FU: 5-fluorouracil; ABC: ATP-binding cassette; ABCG2: ATP-binding cassette subfamily G member 2; ALDH: Aldehyde dehydrogenase; CSCs: Cancer stem cells; EMT: Epithelial-to-mesenchymal transition; EMT-TFs: EMT-inducing transcription factors; IGF1R: Insulin-like growth factor 1 receptor; MET: Mesenchymal-epithelial transition; MiRNAs: MicroRNAs; RAC1: Ras-related C3 botulinum toxin substrate 1; YAP1: Yes-associated protein 1.

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**Availability of data and materials**

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

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**Competing interests**

The authors declare that they have no competing interests.

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