Exploring and exploiting the fundamental role of microRNAs in tumor pathogenesis

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Abstract: miRNAs (miRs) are short RNA molecules that are involved in the posttranscriptional regulation of mRNA. The roles of miRs in tumor pathogenesis have only recently become a focus of research. It is becoming increasingly clear that miRs are important regulators of apoptosis, proliferation, invasion, and metastasis in cancer cells during cancer genesis and progression, furthering our understanding of cancer. In the present review, we summarize and evaluate the recent advances in our understanding of the characteristics of miRs as well as their regulated functions in cancer stem cells (CSCs), the epithelial-mesenchymal transition (EMT), and the tumor microenvironment (TM), describing their roles in tumor pathogenesis and their possible use as new therapeutic targets and biomarkers.

Keywords: miRNA, cancer stem cell, epithelial-mesenchymal transition, tumor microenvironment

Introduction
miRNAs (miRs) are a critical class of small, non-coding, endogenous RNAs that have been implicated in the regulation of gene expression regulation. Since 1993, when Lee et al discovered the miR family member lin-4 in Caenorhabditis elegans, the roles of miRNAs in various diseases have been investigated. To date, approximately 1,872 precursors and 2,578 mature miRs have been identified in Homo sapiens. Approximately 21–25 nucleotides in length, miRs are a group of short, single-stranded RNAs that are widely expressed in eukaryotes. miRs lack an open reading frame, and thus do not encode proteins. The majority of miRs are evolutionarily conserved among distantly related organisms and may be expressed in a tissue-specific or developmental stage-specific manner. Growing evidence indicates that miRs play critical roles in cancer pathogenesis, chemo/radiotherapy resistance, tumor relapse, and metastasis. In recent years, the number of reports regarding cancer-related miRs has increased dramatically. Cancer stem cells (CSCs) and the epithelial-mesenchymal transition (EMT) play pivotal roles in cancer pathogenesis. In this review, we summarize the recent major findings regarding the miRNA-mediated regulation of CSCs, the EMT, and the tumor microenvironment (TM). Progress in this area has important implications for the development of novel targeted therapeutics.

miRs and CSCs
CSCs have been identified in a variety of hematological and solid malignancies and play important roles in tumor initiation, maintenance, progression, metastasis, and chemo/radiotherapy resistance. Increasing evidence suggests that miRs differentially
regulate many properties of CSCs.\textsuperscript{4} Identification of CSC-related miRs and illustration of their intrinsic molecular regulative mechanisms may provide a better understanding of CSCs. The miR-17-92 polycistron, the first reported oncormi, is often amplified and overexpressed in leukemias,\textsuperscript{5} medulloblastomas,\textsuperscript{6} lung cancer,\textsuperscript{7} and nasopharyngeal carcinomas,\textsuperscript{8} and has been reported to play an oncogenic role by regulating various signaling pathways, including the c-myc, hypoxia-inducible factor 1\(\alpha\) (HIF-1\(\alpha\)), and hedgehog signaling pathways.\textsuperscript{6,7} The first reported tumor suppressive miR was the miR-15/miR-16 cluster, which is often deleted in chronic lymphocytic leukemia (CLL), resulting in Bcl-2 accumulation.\textsuperscript{9} An increasing number of reports regarding oncomiRs and tumor suppressive miRs have been released recently, and in depth mechanistic studies are ongoing. In the current review, we discuss CSC-related miRs in several representative cancers.

Among the various solid cancers, the study of breast cancer stem cells (BCSCs) began relatively early and has been extensive. Let-7, miR-30, miR-16, miR-107, and miR-20b were the first miRs identified to be downregulated in BCSCs.\textsuperscript{10,11} More recently, the miR-200c-141, miR-200b-200a-429, and miR-183-96-182 clusters were also identified to be significantly downregulated among the 37 differentially expressed miRs in BCSCs.\textsuperscript{12} By performing a miR microarray profiling analysis of breast CSCs in comparison to non-CSC populations, Okuda et al\textsuperscript{13} recently found that miR-7 is significantly downregulated in metastatic BCSCs. Okuda et al further established a nude mouse metastasis model and reported that miR-7 specifically blocks brain, but not bone, metastasis by modulating KLF4, a gene that is essential for the induction of pluripotent stem cells. Experiments on a series of breast cancer cell lines representing different stages of differentiation revealed that miR-93, a member of the miR106b-25 cluster, negatively regulates the proliferation and differentiation of BCSCs.\textsuperscript{14} A renal cancer study published in 2013 demonstrated that the forced expression of miR-141 inhibits cancer cell proliferation by targeting cell division cycle 25B phosphatase.\textsuperscript{15} However, because most of these studies focused on deregulated miR profiles, verification of alterations in the expression of validated target genes required further study. Fortunately, recent studies have done just that.

Prostate cancer (PCAs) is the most common cancer of the male reproductive system. A decrease in the miR-106b-25 cluster was observed in both primary tumors and distant metastases with early disease recurrence. Subsequent experiments were performed to identify miR-106b-induced global expression changes, and caspase-7 was identified as the target gene.\textsuperscript{16} Another recent prostate cancer study identified 25 upregulated miRs and 36 downregulated miRs in PC-3 sphere cells as compared to adherent cells. Of these dysregulated miRs identified by microarray, miR-143 was validated as the most significantly differentially expressed miR using qRT-PCR. Further analyses suggested that miR-143 may promote prostate cancer metastasis by targeting fibronectin type III domain containing 3B.\textsuperscript{17} CSCs often manifest as spheroid organotypic cultures and have a strong ability to form colonies. Huang et al found that increased levels of miR-143 and miR-145 are associated with decreased cell viability, colony formation, sphere formation, and expression of CSC markers in PC-3 cells from PCa bone metastases, suggesting that decreases in miR-143 and miR-145 in PCa may contribute to PCa bone metastasis by regulating CSC characteristics.\textsuperscript{18} A recent study by Hsieh et al demonstrated that miR-320 is significantly downregulated in PCa cells and is a negative regulator of PCa. They observed that increased levels of miR-320 correlate with a decrease in the CSC properties of PCa cells. CD44 is a molecular marker of CSCs. Through global gene expression profiling, members of the Wnt/catenin signaling pathway and CSC markers were confirmed to be targets of miR-320.\textsuperscript{19} Similarly, miR-708 was identified to be downregulated in a CD44+ subgroup of PCa cells and was proposed to be a tumor suppressor miR, regulating PCa initiation and progression by targeting CD44 and the serine/threonine kinase AKT2.\textsuperscript{20} Downregulation of miR-708 was also demonstrated in the lymph nodes and distal metastases in breast cancer, suggesting a metastasis-suppressive role for breast cancer by targeting the endoplasmic reticulum protein neuronatin.\textsuperscript{21}

By examining the miR profiles of stem and non-stem cells in glioblastoma (GBM), a 2008 study determined that miR-451, miR-486, miR-425, miR-16, miR-107, and miR-185 are consistently downregulated in GBM CSCs.\textsuperscript{22} A recent study by Guessous et al\textsuperscript{23} indicated that the expression of miR-10b is increased in GBM tissues and CSCs. Inhibition of miR-10b strongly reduces the invasion and migration of GBM cells, suggesting that it has an oncogenic role. In contrast, miR-204 and miR-125b were demonstrated to be tumor-suppressive regulators of the development of stem cell phenotypes and cell motility in malignant GBM cells and to be markedly downregulated in glioma stem cells.\textsuperscript{24,25} Through a differential miRNA expression screen, miR-204 was found to be significantly downregulated in glioma CSCs and to act as a tumor suppressor miR by targeting the stemness-governing transcription factor SOX4.
and the migration-promoting receptor EphB2. Chan et al illustrated that miR-138 plays a vital role in promoting the proliferation and apoptosis of GBM CSCs. Overexpression of miR-34a in CD44+ PCa cells exerts pronounced inhibitory effects on prostate metastasis establishment, migration, and metastasis. Similar results were reported in pancreatic cancer. The expression of miR-34a in glioma stem cells was also significantly decreased. Yang et al revealed that decreased levels of miR-34a correlate with increased metastatic activity in breast cancer cells and lymph node metastasis, suggesting that an increase in miR-34a could contribute to metastases by targeting Fos-related antigen 1. 

Pagliuca et al reported that miR-143 and miR-145 are significantly downregulated in colorectal tumor cells and that restoration of their expression levels decreases colorectal tumor proliferation, migration, and chemoresistance. Additionally, they showed that miR-143 and miR-145 function as tumor suppressors by regulating CD44, Kruppel-like factor 5 (KLF5), Kirsten rat sarcoma 2 viral oncogene homolog (KRAS), and v-Raf murine sarcoma viral oncogene homolog B1 (BRAF). However, another study reported that miR-143 and miR-145 are targeted by TARBP2 to regulate Ewing's sarcoma family tumor CSC clonogenicity and tumor maintenance. The downregulation of miR-145 in osteosarcoma tissues was recently shown to be correlated with advanced clinical stage, positive distant metastasis, and negative prognosis.

A glioma study indicated that miR-124 is downregulated in both glioma tissues and cell lines. Through an integrated bioinformatics analysis and experimental confirmation, Xia et al identified SNAI2 as a potential direct target of miR-124, thereby restricting stem-like properties. In a study of pancreatic cancer, Wang et al reported that miR-124 is silenced by hypermethylation in tumor tissues and that miR-124 inhibits cell proliferation, invasion, and metastasis by targeting Rac 1 and inactivating the M KK4-JNK-c-Jun pathway. A recent ovarian cancer study reported a decrease in miR-29 in cisplatin-resistant cells and showed that the ectopic expression of miR-29 reduces the tumorigenicity of cancer cells. In breast tumors, miR-29 is significantly downregulated in the CD44+ cell population and is regulated by the female hormone progesterone (P4). miR-29 expands breast tumor CSC properties by directly targeting Kruppel-like factor 4 (KLF4). Wang et al found that during bone formation, downregulation of NFkappaB and YY1 inhibits miR-29 expression. In human rhabdomyosarcoma cells, activation of the NF-kappaB/YY1 signaling pathway often causes miR-29 silencing. However, resumption of the expression of miR-29 results in the inhibition of tumor growth and differentiation. Zhang et al recently demonstrated that miR-29 is downregulated by MYC through the MYC-EZH2-miR-29 axis and participates in lymphomagenesis. A study conducted by Zhang et al revealed the increased expression of has-miR-150, has-miR-152, has-miR-888, has-miR-519e, and has-miR-532-5p in CD133-hepatocellular carcinoma (HCC). Moreover, this group demonstrated that the overexpression of miR-150 correlates with significant reductions in CSCs, which are mediated through the negative regulation of c-Myc.

Numerous miR profiling and characterization studies have identified critical roles for miRs in cancer pathogenesis; miR-based therapeutics target CSCs by correcting their aberrant miR expression levels, restoring their suppressive functions and/or blocking their oncogenic properties via the RNAi pathway. Jin et al reported that Let-7 is downregulated in HCC tissues and cells. Another study revealed an increase in Let-7 in HCC stem cells in comparison to HCC cell lines and normal liver stem cells. This increase was found to be associated with decreased chemosensitivity to sorafenib and doxorubicin, possibly through the caspase-3-STAT3 pathway. Additionally, miR-181 was identified to play a pivotal role in the regulation of the oncogenic effects of Twist in human HSC invasion by targeting TIMP-3 and NLK. In another study conducted by Xia et al, silencing of miR-214 in EpCAM+ HCC tumor cells was shown to increase the population of these cells by activating the β-catenin pathway. Upregulation of miR-214 was also reported to be related to chemoresistance and metastasis. Xu et al reported that the expression level of miR-214 positively correlates with the proliferation of ovarian CSCs through its regulation of p53-Nanog signaling pathway.

miR-125b-2 is overexpressed in glioblastoma tissues and glioblastoma stem cells (GSCs) and is downregulated following GSC-induced chemosensitivity to temozolomide. miR-21, as an oncomiR identified in glioblastoma, may be another promising chemotherapeutic target. Zhang et al reported that a miR-21 inhibitor sensitizes human GSCs to temozolomide. By transfecting the has-miR-21 antagomiR into breast cancer cells, Han et al found that antagonism of miR-21 could reverse the EMT and decrease the migration and invasion of breast cancer cells. Moreover, antagonism of miR-21 decreases the formation of mammospheres and reduces CSC characteristics by regulating phosphatase and tensin homolog (PTEN) and inactivating the AKT and ERK1/2 pathways in breast cancer.

miR-145, a tumor suppressor miR, is downregulated in lung cancer, nasopharyngeal carcinoma, gastric
miRs and the EMT

The EMT may be the first step in the invasion and metastasis of solid cancers and is related to therapy resistance. Many reports have also linked the EMT to the induction of CSCs in various cancers. Increasing numbers of miRs have been demonstrated to act as critical modulators of the EMT. Members of the miR-200 family function as tumor suppressors in many types of cancers and have been previously reported to prevent the EMT in several solid cancers, including breast cancer, colorectal cancer, bladder cancer, prostate cancer, glioma, and metastatic melanoma. MiR profiling microarray technology, combined with quantitative PCR validation, demonstrated that miR-1275 is significantly downregulated during GSC differentiation, and inhibition of miR-1275 in GSCs suppresses their proliferative ability. MiR-200c, which targets BIM1, demonstrated a similar tumor suppressor role in melanoma, prostate cancer, and head and neck squamous cell carcinomas.

miR-128 functions as a tumor suppressor in breast cancer and glioma. Using lentivirus-mediated miR-128 transduction in breast CSCs, miR-128 expression levels were demonstrated to sensitize breast CSCs to doxorubicin by regulating BMI-1 and ABCG5. Moreover, miR-128 reduction in tissues is correlated with poor prognosis. Qian et al demonstrated a decrease in miR-128-2 results in the induction of oncogenic transformation by targeting BMI-1, CSF1, KLF4, LIN28A, NANOG, and SNAI1 through the PI3K/AKT and STAT3 signaling pathways in breast cancer.

miR-128 is downregulated during the EMT process and may target SNAI1 and ZEB2. In stable has-miR-191-overexpressing cells, overexpression of has-miR-191 was found to induce the EMT, inhibit pan-cytokeratin and E-cadherin, and upregulate N-cadherin by negatively regulating TIMP3. Xu et al reported that miR-148a suppresses the EMT in HCC cells by inhibiting HP1P expression, possibly through the AKT or ERK/mTOR signaling pathway. The results of this study revealed that miR-148a increases the expression of E-cadherin and downregulates the expression of SNAI1, N-cadherin, and Vimentin. Using cell adhesion assays, Yan et al found that miR-10b suppresses HCC cell-matrix adhesion and is involved in the metastatic process by regulating the Eph tyrosine kinase receptor A4-mediated EMT. Several studies have demonstrated the decreased expression of miR-214 in HCC. Using real-time PCR experiments, luciferase reporter assays and Western blot analyses, we demonstrated that a decreased level of miR-214 in metastatic intrahepatic cholangiocarcinoma (ICC) tissues is correlated with an increased level of Twist, suggesting that a decrease in miR-214 may also promote the EMT in ICC cells by targeting Twist.

In breast cancer, numerous miRs have been associated with the EMT, including miR-9, Let-7, miR-200 and miR-24. The miR-106b-25 cluster plays an important role during oncogenesis in breast cancer. Overexpression of the miR-106b-25 cluster activates TGF-beta signaling and induces the EMT. Tellingly, this cluster of miRs also induces a population of cells with a CSC phenotype in a transgenic mouse model. miR-124 has been reported to be decreased in breast cancer, glioma, oral squamous cell carcinomas, and HCC. In addition to playing an important role in the regulation of CSC properties, miR-124 also regulates the EMT in breast cancer by targeting the E-cadherin transcriptional repressor Slug. By establishing a tamoxifen-resistant breast cancer model and conducting a subsequent genome-wide miR microarray analysis, Ward et al found that decreases in miR-375 contributed to tamoxifen resistance by regulating the EMT.

In lung cancer, miR-23a modulates EMT by targeting E-cadherin, and induces chemoresistance to gefitinib. By a screen of a natural epithelial-mesenchymal phenotype cell line pair and a TGF-β-induced EMT cell model with a miR array, Xu et al revealed that miR-153 is significantly downregulated during the EMT process and may target SNAI1 and ZEB2. Hamada et al demonstrated that the
increase in miR-197 in pancreatic cancer induces the EMT by regulating p120 catenin. By comparing the miR expression profiles of HCC tissue from patients with early-recurrent disease to those with non-recurrent disease, Xia et al found that an increase in miR-216a/217 in the early-recurrent group was associated with EMT and CSC properties by targeting SMAD7 and PTEN. Furthermore, they demonstrated that overexpression of miR-216a/217 activates the TGF-β signaling pathway and induces chemoresistance to sorafenib by targeting the PI3K-Akt signaling pathway. A 2012 study showed that the miR-200c expression level is negatively correlated with the EMT and invasion in ICC cells by targeting neural cell adhesion molecule 1.

Expression analyses revealed that the miR-200 family and miR-205 are decreased in EMT models and function negatively by targeting ZEB1 and SIP1. Recently, miR-200c and miR-205 were reported to regulate the EMT in prostate cancer cells by targeting ZEB1 and ZEB2, resulting in docetaxel resistance and the overexpression of CSC markers. miR-205 expression was also demonstrated to be regulated by p63 and to enhance the migration and metastasis of prostate cancer cells. Ru et al found that miR-29b is commonly downregulated in prostate cancer and functions as an anti-metastatic miR by regulating the EMT. Ectopic expression of miR-29b in PCa cells induces E-cadherin expression and decreases the expression of N-cadherin, Twist, and SNAIL. Using a PTEN- and TP53-null PCa model, a recent study showed that both increased levels of Slug and decreased levels of miR-1 and miR-200 are required to initiate the EMT, and that Slug is regulated by miR-1 and miR-200b.

miR-34 has been putatively reported to function as a tumor suppressor miR in many tumors, including colorectal cancer, pancreatic cancer, breast cancer, ovarian cancer, urothelial cancer, renal cell carcinoma, and soft tissue sarcomas. miR-34c expression is decreased in breast CSCs, and restoration of its expression inhibits mammosphere formation, CSC phenotypes, and the EMT in breast CSCs by silencing Notch4. Siemens et al reported that the enforced expression of miR-34a induces the MET, downregulates SNAIL, and inhibits the TGF-β–induced EMT. Through integrated genomic analyses of 459 serous cases and subsequent functional experiments, a recent ovarian cancer study identified and validated miR-506 as an EMT inhibitor and positive prognostic predictor in ovarian cancer by targeting SNAI2. Enhanced expression of miR-506 upregulates E-cadherin expression, suppresses the EMT, and reduces cancer cell proliferation, migration, and invasion.

miRs and TM

The interaction between cancer cells and the TM plays a critical role in tumor genesis, maintenance, and progression. The TM directly influences tumor cells and acts as an important contributor to cancer progression and metastasis. CSC properties and EMT-related pathways are strongly influenced by the TM. The TM contains the extracellular matrix and various cell types, including fibroblasts, endothelial cells, and immune cells. Dysregulated miRs in the TM could regulate tumor proliferation, invasion, and metastasis.

Several studies have suggested that miRs acting as oncogenes or tumor suppressor genes in cancer-associated fibroblasts (CAFs) regulate tumor progression based on the secretion of certain growth factors and matrix metalloproteinases (MMPs). Chou et al reported that GATA3 promotes miR-29b expression and suppresses lung metastases in breast cancer. They further identified miR-29b sites in the 3′ UTRs of TGF-β and many TM-related genes, including VEGF, ANGPTL4, PDGF, LOX, and MMP9, suggesting a metastatic suppressor role for miR-29 by modulating the TM. Another miR-29 family member, miR-29c, was also shown to alter the TM in nasopharyngeal carcinoma, leading to the dysregulation of 10 extracellular matrix component genes. In breast cancer, miR-320, which is regulated by PTEN, was demonstrated to be a critical regulator of the TM in CAFs and was shown to regulate the secretome of MMP9 and EMILIN2, which are involved in the regulation of angiogenesis. The miR-200 family has been demonstrated to play a critical role in the regulation of the EMT and CSC properties. In lung adenocarcinoma, increases in miR-200 are correlated with alterations in the TM, inhibition of metastasis, increases in extracellular matrix proteins (CDH1, EPS8 L2, IRF2BP2, KRT7, KRT8, and KRT19) and peptidases, and alterations in the distribution of cell adhesion proteins in metastatic cell lines. In PCa, downregulation of miR-15 and miR-16 in CAFs regulates the TM by reducing the repression of Fgf-2 and its receptor, Fgfr1, which forms a molecular circuitry that promotes tumor expansion and invasiveness.

In addition to CAFs, other cells in the TM also display important regulatory roles during tumor progression. With respect to glioma, in the microvascular epithelial cells of the human brain, miR-296 interacts with the 3′ UTR of hepatocyte growth factor, downregulating its expression and promoting angiogenesis. Immune cells are critical components of the TM. By analyzing the clinicopathological data from 288 HCC patients, Yang et al revealed that hepatitis B virus (HBV) infection is strongly associated with the development of portal venous tumor thrombi (PVT) and poor
prognosis. Subsequent experiments were performed on HCC cell lines and tissue samples, and miR-34a was identified to be associated with HBV-initiated HCC during the development of PVTT, which is negatively regulated by TGF-β. This study further demonstrated that the ectopic expression of miR-34a significantly decreases the recruitment of Treg cells in the TM by regulating the expression of the chemokine CCL22. After conducting a series of experiments using transgenic mice, Dudda et al. reported that the intrinsic expression of miR-155 promotes proliferation and limits apoptosis in effector CD8+ T cells. In addition, this study demonstrated that enforcing miR-155 expression augments the antitumor activity of CD8+ T cells. miRs have also been reported to interact with natural killer (NK) cells. A 2013 study demonstrated that miR-122 enhances the antitumor activity of NK cells, controlling tumor development by regulating the TLR signaling pathway. Dendritic cells (DCs) were also suggested to be regulated by miRs. Min et al. found that tumor-associated miRs, including miR-22 and miR-503, regulate the survival and longevity of DCs; miR-22 was found to target YWHAZ, and miR-503 was found to target Bcl2. After identifying the miR expression pattern in tumor-associated macrophages in a mouse breast cancer model, Yang et al. demonstrated that miR-19a-3p inhibits the metastasis of cancer cells by suppressing M2 macrophage function by targeting Fra-1.

Hypoxia is an important feature of the TM. Several miRs were identified to be dysregulated in response to hypoxic conditions in the TM. miR-495 was identified to be a hypoxia-induced miR in breast CSCs, where it suppresses E-cadherin expression and promotes the EMT. By conducting experiments on pancreatic cancer cell lines using stem-loop RT-PCR, WST-1 assays, and flow cytometry, Mace et al. found that the expression of miR-21 is induced by hypoxia in pancreatic cancer cells, facilitating apoptosis evasion. Another group found that miR-210 is induced not only during hypoxia but also during iron deficiency. This study further identified that the expression of miR-210 is associated with chronic hypoxia in the TM, suggesting a modulatory role of miR-210 during apoptosis and proliferation in cancer cells in the chronic hypoxic TM. Despite the dysregulated expression of miRs that is induced by hypoxia in the TM, progress has been made in our understanding of the molecular mechanism underlying the miR biogenesis machinery. The EGFR was recently demonstrated to suppress the maturation of specific

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tumor suppressor miRs by phosphorylating argonaute 2 and reducing the binding of Dicer and argonaute 2 in the hypoxia TM.\textsuperscript{114} Using bioinformatics in conjunction with experimental validation, Chen et al discovered that Let-7 and miR-103/107 are induced by hypoxia in vascular endothelial cells and consequently target argonaute 1 in miRISC, resulting in the reversal of the suppression of VEGF expression, enhanced angiogenesis, and tumor progression.\textsuperscript{115}

Conclusion

In summary, miRs are closely related to tumors. miRs regulate tumor occurrence and development by affecting related genes and signal pathways, and this process results in changes in miR expression (as shown in Table 1). After further research, miRs are expected to be used for early tumor diagnoses and as therapeutic targets and prognostic indicators. Understanding the molecular mechanism underlying cancer-related miRs in tumor pathogenesis is of paramount importance in providing new avenues for intervention.

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Disclosure

The authors report no conflicts of interest in this work.

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