MicroRNAs: regulators of cancer metastasis and epithelial-mesenchymal transition (EMT)

Xiang-Ming Ding

Abstract
Tumor metastasis is the main cause of death in patients with solid tumors. The epithelial-mesenchymal transition (EMT) process, in which epithelial cells are converted into mesenchymal cells, is frequently activated during cancer invasion and metastasis. MicroRNAs (miRNAs) are small, non-coding RNAs that provide widespread expressional control by repressing mRNA translation and inducing mRNA degradation. The fundamental roles of miRNAs in tumor growth and metastasis have been increasingly well recognized. A growing number of miRNAs are reported to regulate tumor invasion/metastasis through EMT-related and/or non-EMT-related mechanisms. In this review, we discuss the functional role and molecular mechanism of miRNAs in regulating cancer metastasis and EMT.

Key words: MicroRNA (miRNA), cancer metastasis, EMT

Metastasis, the process by which cancer cells spread from a primary site to other parts of the body, causes approximately 90% of cancer-related deaths[1]. The underlying molecular and cellular mechanism of cancer metastasis is still largely unknown.

Epithelial-mesenchymal transition (EMT) is considered an early and key step in the metastatic cascade[2]. EMT is an evolutionarily conserved program in which cells lose their epithelial features and acquire mesenchymal properties through a process involving cytoskeleton remodeling and cell morphologic changes, resulting in increased invasiveness[3]. EMT is regulated by a variety of signaling pathways that originate from the tumor stroma, including transforming growth factor-β (TGF-β), hepatocyte growth factor (HGF), and epidermal growth factor (EGF)[4]. A hallmark of EMT is the loss of E-cadherin (CDH1), a transmembrane glycoprotein that forms the core of adheren junctions between adjacent epithelial cells and plays a critical role in cell-to-cell adhesion[5,6]. A family of E-box–binding transcription factors, including snail family zinc finger 1 (SNAI1), snail family zinc finger 2 (SNAI2), zinc finger E-box–binding homeobox 1 (ZEB1), zinc finger E-box–binding homeobox 2 (ZEB2), and twist basic helix-loop-helix transcription factor 1 (TWIST1), have been reported to induce EMT and tumor metastasis by repressing CDH1[7].

MicroRNAs (miRNAs) are endogenously expressed, small, non-coding RNAs that regulate a variety of biological processes by modulating gene expression at the post-transcriptional level[8]. It is estimated that more than one third of human genes are targeted by miRNAs. Growing evidence shows that miRNAs play an important role in the control of tumor growth and progression[9,10]. Some miRNAs act as oncogenes and some, tumor suppressors, with both classes termed oncomirs[10]. More importantly, miRNAs are also master regulators of EMT and dynamically regulate the balance between EMT and the reverse process, MET. In this review, we focus on the molecular mechanism through which miRNAs regulate EMT and cancer metastasis.

Regulation of Cancer Metastasis by Anti-EMT miRNAs

In 2008, four different groups identified the miR-200 family, which includes miR-200a, miR-200b, miR-200c, miR-141, and miR-429, as a new epithelial marker and regulator of EMT[11-14]. By comparing miRNA expression between epithelial and mesenchymal cells in different cell models, all four groups found that the miR-200 family is highly expressed in epithelial cells. Loss-of-function and gain-of-function analysis showed that miR-200 regulates the EMT and MET processes. Further analysis of the molecular mechanism revealed a double negative feedback loop between the miR-200 family and ZEB1 and ZEB2. Specifically, miR-200 represses ZEB1/ZEB2 expression by directly binding their 3’ UTRs, and ZEB1/ZEB2 inhibits miR-200 transcription by binding its promoter[15,16]. Interestingly, two recent studies identified another feedback loop between miR-203 and SNAI1/SNAI2 that also regulates EMT and cancer metastasis[18,19]. Both miR-200 and miR-203 are down-regulated during in vitro EMT induced by TGF-β, and this down-regulation is indispensable for EMT.
Importantly, miR-200 and miR-203 are significantly down-regulated in the mesenchymal component of endometrial carcinosarcoma, which represents a bona fide example of EMT in vivo, and in claudin-low type breast cancer, which contains a majority of mesenchymal-like cells[18,19].

Accumulating evidence shows that EMT-associated transcription factors such as SNAI1/SNAI2 and ZEB1/ZEB2 regulate each other’s expression, thus facilitating EMT[7]. Because SNAI2 also represses miR-200 and ZEB1 also represses miR-203[16,20], these or other miRNAs could be the link between reciprocal regulation of SNAI1/SNAI2 and ZEB1/ZEB2. Also, these two feedback loops seem to share similarity in both upstream inducers and operation modes, further creating the contours of a hierarchical framework that defines cellular plasticity.

Similar to CDH1[21], miR-200 and miR-203 are also regulated by epigenetic mechanisms such as DNA methylation and histone methylation[22-24]. There is an inverse correlation between miR-200 and miR-203 promoter methylation status and gene expression in breast cancer cell lines, which is accompanied by permissive and repressive histone modifications at the promoter corresponding to an epithelial and mesenchymal phenotype, respectively[22,25]. Notably, a recent study showed that DNA methylation of the miR-200 family is dynamic and reversible during EMT induced by TGF-β and may play an important role in regulating plasticity between epithelial and mesenchymal states[26].

In addition to miR-200 and miR-203, other miRNAs have been implicated in EMT and cancer metastasis. For example, miR-34 and miR-30a were shown to inhibit EMT by directly targeting SNAI1, a transcriptional repressor of CDH1[27-29]. Interestingly, both miR-200 and miR-34 are target genes of p53, linking p53 and the EMT program[27,30,31]. p53 induces the expression of miR-200 and/or miR-34, which further represses the expression of ZEB1/ZEB2 and SNAI1/SNAI2 and induces CDH1 expression, thus leading to MET. In addition, miR-612 inhibits EMT through the suppression of AKT2 in hepatocellular carcinoma[22], miRNAs associated with EMT are summarized in Table 1.

Several recent studies demonstrated that the induction of EMT can generate cells with properties of stem cells or cancer stem cells, which are capable of both tumor initiation and sustenance of tumor growth[33,34]. Induction of TGF-β or ectopic expression of EMT-inducing transcription factors in human mammary epithelial cells and transformed mammary cells resulted in the generation of stem-like cells[35]. Emerging evidence indicates that miRNAs control the stemness of cancer stem cells. Shimono et al.[35] showed the down-regulation of miR-200c links breast cancer stem cells with normal stem cells. Namely, miR-200c blocked the expression of BMI1, strongly suppressing mammary duct formation by normal mammary stem cells and breast cancer cell–driven tumor formation. ZEB1 links the activation of EMT and maintenance of stemness in one cell by suppressing the expression of stemness-inhibiting miRNAs, including miR-200, miR-203, and miR-183[20]. Linking EMT and cancer stem cells to specific miRNAs will provide a better understanding of how metastatic cancer arises, and targeting these miRNAs may provide new ways to strike cancer at its root.

### Table 1. MicroRNAs (miRNAs) associated with epithelial-mesenchymal transition (EMT)

| miRNA | Effect on EMT | Upstream regulator(s) | Downstream target(s) | Reference(s) |
|-------|---------------|-----------------------|----------------------|--------------|
| miR-200s | Suppress | ZEB1/2, SNAI1/2, P53 | ZEB1/2, SNAI2 | [11–13, 15, 31] |
| miR-203 | Suppress | ZEB1, SNAI1/2 | SNAI1/2 | [16, 17, 20] |
| miR-204 | Suppress | NA | SNAI2, TGFβR2 | [72] |
| miR-205 | Suppress | TGF-β | ZEB1/2 | [11] |
| miR-34 | Suppress | SNAI1, P53 | SNAI1 | [27, 29] |
| miR-1 | Suppress | SNAI2 | SNAI2 | [73] |
| miR-153 | Suppress | NA | SNAI1, ZEB2 | [74] |
| miR-30a | Suppress | NA | SNAI1 | [28] |
| miR-124 | Suppress | NA | SNAI2 | [75] |
| miR-612 | Suppress | NA | AKT2 | [32] |
| miR-9 | Promote | MYC | CDH1 | [36] |
| miR-103/107 | Promote | NA | DICER1 | [38] |
| miR-221/222 | Promote | FOSL1 | TRPS1 | [39] |
| miR-155 | Promote | SMAD4 | RH0A | [40] |
| miR-181a | Promote | TGF-β | Bim | [41] |
| miR216a/217 | Promote | NA | PTEN, SMAD7 | [42] |
| miR-27 | Promote | NA | APC | [76] |
| miR-197 | Promote | NA | p120 catenin | [77] |
| miR-490-3p | Promote | NA | ERGIC3 | [78] |

NA, not available.
Regulation of Cancer Metastasis by Pro-EMT miRNAs

miR-200 family members and miR-203 are biomarkers of the epithelial and differentiated phenotype and thus are considered inducers of MET. However, there is also evidence for miRNAs promoting the transition to a mesenchymal phenotype. For example, miR-9 directly targets CDH1, leading to increased cell invasiveness and a context-dependent EMT-like conversion[30]. Similarly, increased miR-92a expression reduces CDH1 expression, resulting in the promotion of cancer cell motility and invasiveness[37]. The miR-103/107 family attenuates miRNA biosynthesis by targeting DICER1, a key component of the miRNA processing machinery[38]. At the cellular level, miR-103/107 induces EMT by down-regulating miR-200. Functionally, miR-103/107 confers migratory capacities in vitro and empowers metastatic dissemination of otherwise nonaggressive cells in vivo. miR-221/222, identified as a cluster of basal-like, subtype-specific miRNAs, promote EMT in breast cancer cells by targeting trichorhinophalangeal 1 (TRPS1)--mediated inhibition of ZEB2[39]. miR-155 and miR-81a are induced by TGF-β and promote EMT and cancer invasion[40,41], in contrast to miR-200 and miR-203, which are inhibited by TGF-β. miR-155, which is overexpressed in several malignancies, was reported to be a direct transcriptional target of TGF-β/SMAD4 signaling. miR-155 promotes EMT by targeting RhoA GTPase, which regulates cellular polarity and tight junction formation and stability[42]. miR-81a promotes EMT and cancer metastasis by repressing BIM[43]. In addition, miR-216a/217 induced EMT and promoted drug resistance and recurrence by targeting PTEN and SMAD7 in liver cancer[44]. Taken together, cancer cells exploit these miRNAs to regulate the EMT/MET--associated cancer metastasis by targeting different genes involved in EMT/MET process.

The Regulation of Cancer Metastasis by Non-EMT--Associated miRNAs

Cancer metastasis is a complex, multistep process involving the escape of neoplastic cells from a primary tumor (local invasion), intravasation into the systemic circulation, survival during transit through the vasculature, extravasation into the parenchyma of distant tissues, establishment of micrometastases, and ultimately, outgrowth of macroscopic secondary tumors (colonization)[4]. miRNAs are well suited to regulate cancer metastasis because of their capacity to coordinately repress numerous target genes, thereby potentially enabling their intervention at multiple steps of the invasion-metastasis cascade[45]. miR-31 is one such multi-functional miRNA that acts by repressing a cohort of pro-metastatic targets including RHOA, radixin (RDX), and integrin α5 (ITGAV)[46]. In addition to miR-31, several other anti-metastatic miRNAs have been identified in a number of cancers, as summarized in Table 2. miR-335 and miR-126 were the first two miRNAs found to suppress metastasis in human breast cancer[47], miR-335 suppresses metastasis and migration by targeting SOX4 and tenasin (TNC), whereas miR-126 targets SDF1A to inhibit cell proliferation, adhesion, and migration[48,49]. Let-7 is widely viewed as a tumor suppressor[50]. Consistent with this, the expression of let-7 family members is down-regulated in many cancer types compared with normal tissue, as well as during tumor progression[51]. Upon restoration in breast cancer stem cells, let-7 inhibited mammosphere-forming ability in vitro and metastatic ability in vivo by targeting RAS and high mobility group AT-hook 2 (HMG2)[52,53]. There is also a very clear link between loss of let-7 expression and the development of poorly differentiated, aggressive cancers. miR-191/425 cluster, which is induced by estrogen receptor alpha (ERα), reduced cell proliferation and impaired tumorigenesis and metastasis by repressing SATB1, CCND2, and FSCN1 in breast cancer[54], miR-33a suppresses bone metastasis in lung cancer by targeting parathyroid hormone-like hormone (PHERP), a potent stimulator of osteoclastic bone resorption[55].

In addition to anti-metastatic miRNAs, a number of miRNAs are pro-metastatic. miR-21 was one of the first miRNAs to be described as an oncomir[56,57]. Because most of the targets of miR-21, including programmed cell death 4 (PDCD4), PTEN, tropomyosin 1 (TPM1), and RHOB, are tumor suppressors, miR-21 has been associated with a wide variety of cancers[54,55]. For example, miR-21 was found to promote invasion, intravasation, and metastasis in ovarian cancer and colon cancer[56,57]. miR-10b, which is induced by TWIST, positively regulates cell migration and invasion by targeting HOXD10, a repressor of pro-metastatic genes such as RHOC, plasminogen activator, urokinase receptor (PLAUR), and matrix metalloproteinase 14 (MMP14)[58,59]. Clinically, the level of miR-10b expression in primary breast carcinomas associates with cancer progression[60]. In addition, miR-10b promotes metastasis of hepatocellular and esophageal carcinomas by targeting cell adhesion molecule 1 (CADM1) and Kruppel-like factor 4 (KLF4), respectively[61,62]. miR-10a was found to be a key mediator of metastatic behavior in pancreatic cancer, exerting its effects by suppressing homeobox B1 (HOXB1) and homeobox B3 (HOXB3)[63]. Inhibiting miR-10a expression (with retinoic acid receptor antagonists) or function (with specific inhibitors) is a promising starting point for anti-metastatic therapies. miR-373 and miR-520c stimulate tumor cell migration and invasion, at least in part through direct suppression of CD44, mechanistic target of rapamycin (mTOR), and sirtuin 1 (SIRT1)[64,65]. Also, miR-373 expression is significantly higher in metastatic tumors than in non-metastatic tumors[66]. Interestingly, although miR-200 was not reported as an anti-EMT miRNA that inhibits tumor invasion, a recent study by Korpal et al.[67] showed that miR-200 promotes metastatic colonization by targeting Sec23 homolog A (Sec23a). Altogether, miRNAs regulate cancer metastasis through the inhibition of the genes involved in different steps of the cancer metastasis cascade.

miRNAs as Novel Targets for Cancer Therapy

Because miRNAs play a critical role in tumor formation, maintenance, and progression, intensive efforts have been made to develop miRNA-based therapeutic strategies for cancer treatment. It was only 10 years ago that the first human miRNA was discovered, yet an miRNA-based therapeutic has already entered phase 2 clinical trials[68]. This rapid progression from discovery to development promises to yield an attractive new class of therapeutics. Mimics of let-7 and miR-34 are under preclinical development to target a broad
spectrum of solid tumors. Therapeutic delivery of let-7—either in the form of a let-7 mimic or a virus—leads to a robust inhibition of tumor growth in human non–small cell lung cancer xenografts and the KRAS-G12D transgenic mouse model [67,68]. Similarly, systemic delivery of the miR-34 mimic blocked tumor growth in mouse models of lung and prostate cancers [69,70]. Conversely, several studies show that miRNAs can be targeted therapeutically to suppress metastasis. For example, Ma et al. [71] demonstrated that systemic treatment of tumor-bearing mice with miR-10b antagomirs, a class of chemically modified anti-miRNA oligonucleotides, suppressed breast cancer metastasis. These antagonists did not reduce primary mammary tumor growth but markedly suppressed formation of lung metastases in a sequence-specific manner [71].

**Table 1. miRNAs associated with tumor metastasis (non-EMT)**

| miRNA Effect on metastasis | Upstream regulator | Downstream target(s) | Cancer type(s) | Reference(s) |
|---------------------------|--------------------|----------------------|----------------|--------------|
| miR-31 Suppress NA        | RHOA, RDX, ITGA5   | Breast               | [44]           |
| miR-335 Suppress NA       | SOX4, TNC          | Breast, gastric      | [45]           |
| miR-126 Suppress NA       | SDF1α              | Breast,             | [45, 46]       |
| let-7 Suppress LIN28,MYC  | RAS, HMG1A2        | Breast, colon       | [49, 50]       |
| miR-191/425 Suppress ERα  | SATB1, CCND2, FSCN1| Breast              | [51]           |
| miR-33a Suppress TTF1      | PTHrP, HMG1A2      | Lung                | [52, 79]       |
| miR-363 Suppress NA       | PDPN               | Head and neck       | [80]           |
| miR-218 Suppress EZH2     | UGT8               | Pancreatic          | [81]           |
| miR-29b Suppress GATA3    | EGFA, ANGPTL4, PDGF, LOX, MMP9, ITGA6, ITGB1, TGFB | Breast | [82] |
| miR-195 Suppress NA       | IKKα, TAB3         | Liver               | [83]           |
| miR-148a Suppress HBx     | HPIP               | Liver               | [84]           |
| miR-290 Suppress Arid4b   |                    | Breast              | [85]           |
| miR-137 Suppress HMG1A1   | FMNL2              | Colorectal          | [86]           |
| miR-138 Suppress NA       | SOX4, HIF-1α       | Ovarian             | [87]           |
| miR-140-5p Suppress NA    | TGFB1, FGF9        | Liver               | [88]           |
| miR-143 Suppress ERK5, AKT|                    | Bladder, esophageal | [89, 90]       |
| miR-218 Suppress NA       | CAV2               | Renal               | [81]           |
| miR-23b/27b Suppress NA   | RAC1               | Prostate            | [91]           |
| miR-7 Suppress NA         | KLF4               | Breast              | [92]           |
| miR-26a Suppress NA       | EZH2               | Nasopharyngeal      | [93]           |
| miR-29c Suppress NA       | TIAM1              | Nasopharyngeal      | [94]           |
| miR-30a Suppress NA       | PIK3CD             | Colorectal          | [95]           |
| miR-145 Suppress NA       | ADAM17, FBSCN1     | Melanoma, liver     | [96, 97]       |
| miR-148b Suppress NA      | AMPKα1             | Pancreatic          | [98]           |
| miR-194 Suppress NA       | BMP1, p27          | Lung                | [99]           |
| miR-520h Suppress NA      | Resveratrol        | Lung                | [100]          |
| miR-22 Suppress NA        | TIAM1              | Colon               | [101]          |
| miR-100 Suppress NA       | mTOR               | Bladder             | [102]          |
| miR-145 Suppress NA       | COL5A1, Ets1       | Meningiomas, gastric| [103, 104]    |
| miR-122 Promote NA        | CAT1               | Colorectal          | [105]          |
| miR-1908 Promote NA       | ApoE, DNAJ4        | Melanoma            | [106]          |
| miR-199a-5p Promote NA    | ApoE, DNAJ4        | Melanoma            | [106]          |
| miR-199a-3p Promote NA    | ApoE, DNAJ4        | Melanoma            | [106]          |
| miR-10b Promote Twist     | HOXD10, CADM1, RHOB, KLF4, TIAM1 | Breast, liver, esophageal, glioma | [58–61] |
| miR-21 Promote NA         | PTEN, PDCD4, TPM1  | Breast, colon       | [53–55]        |
| miR-550a Promote NA       | CPEB4              | Liver               | [107]          |
| miR-24 Promote NA         | PTPN9, PTPRF       | Breast              | [108]          |
| miR-373 Promote NA        | CD44, mTOR, SIRT1  | Breast, fibrosarcoma| [63, 64]       |
| miR-520c Promote NA       | CD44, mTOR, SIRT2  | Breast, fibrosarcoma| [63, 64]       |
| miR-93 Promote NA         | LATS2              | Breast              | [109]          |

NA, not available.

**Perspective**

Bioinformatic prediction and experimental validation have revealed that many miRNAs and their target genes are involved...
in cancer metastasis (Tables 1 and 2). However, the upstream regulators of these miRNAs still remain elusive. Understanding how these oncomirs are regulated will be valuable for promoting or suppressing their expression and thereby for subsequently inhibiting cancer metastasis. The challenge in identifying regulators of mature miRNAs is a lack of information on the sequence of primary miRNAs, which are difficult to amplify because of their low stability and expression levels. However, as next-generation sequencing technology continues to advance, RNA-sequencing will provide novel insight on difficult-to-study primary miRNAs. We anticipate that more upstream regulators of miRNAs will be identified in the future.

Received: 2013-05-15; revised: 2013-07-15; accepted: 2013-08-23.

References
[1] Chaffer CL, Weinberg RA. A perspective on cancer cell metastasis. Science, 2011,331:1559–1564.
[2] Thiery JP. Epithelial-mesenchymal transitions in tumour progression. Nat Rev Cancer, 2002,2:442–454.
[3] Nieto MA. The ins and outs of the epithelial to mesenchymal transition in health and disease. Annu Rev Cell Dev Biol, 2011,27:347–376.
[4] Kalluri R, Weinberg RA. The basics of epithelial-mesenchymal transition. J Clin Invest, 2009,119:1420–1428.
[5] Gumbiner BM. Regulation of cadherin-mediated adhesion in morphogenesis. Nat Rev Mol Cell Biol, 2005,6:622–634.
[6] Onder TT, Gupta PB, Mani SA, et al. Loss of E-cadherin promotes metastasis via multiple downstream transcriptional pathways. Cancer Res, 2008,68:3645–3654.
[7] Peinado H, Olmeda D, Cano A. Snail, Zeb and bHLH factors in cancer. Nat Rev Cancer, 2007,7:415–428.
[8] Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. Cell, 2004,116:281–297.
[9] Stahlhut Espinosa CE, Slack FJ. The role of microRNAs in cancer. Yale J Biol Med, 2006,79:131–140.
[10] Esquela-Kerscher A, Slack FJ. Oncomirs-microRNAs with a role in cancer. Nat Rev Cancer, 2006,6:259–269.
[11] Gregory PA, Bert AG, Paterson EL, et al. The miR-200 family and miR-205 regulate epithelial to mesenchymal transition by targeting ZEB1 and SIP1. Nat Cell Biol, 2008,10:593–601.
[12] Park SM, Gaur AB, Lengyel E, et al. The miR-200 family determines the epithelial phenotype of cancer cells by targeting the E-cadherin repressors ZEB1 and ZEB2. Genes Dev, 2008,22:894–907.
[13] Korpal M, Lee ES, Hu G, et al. The miR-200 family inhibits epithelial-mesenchymal transition and cancer cell migration by direct targeting of E-cadherin transcriptional repressors ZEB1 and ZEB2. J Biol Chem, 2008,283:14910–14914.
[14] Burk U, Schubert J, Wellner U, et al. A reciprocal repression between ZEB1 and members of the miR-200 family promotes EMT and invasion in cancer cells. EMBO Rep, 2008,9:582–589.
[15] Bracken CP, Gregory PA, Kolesnikoff N, et al. A double-negative feedback loop between ZEB1-SIP1 and the microRNA-200 family regulates epithelial-mesenchymal transition. Cancer Res, 2008,68:7846–7854.
[16] Ding X, Park SI, McCauley LK, et al. Signaling between transforming growth factor beta (TGF-beta) and transcription factor SNAI2 represses expression of microRNA miR-203 to promote epithelial-mesenchymal transition and tumor metastasis. J Biol Chem, 2013,288:10241–10253.
[17] Moes M, Le Bechec A, Crespo I, et al. A novel network integrating a miRNA-203/SNAI1 feedback loop which regulates epithelial to mesenchymal transition. PLoS One, 2012,7:e35440.
[18] Herschkowitz JJ, Zhao W, Zhang M, et al. Comparative oncomics identifies breast tumors enriched in functional tumor-initiating cells. Proc Natl Acad Sci U S A, 2012,109:2778–2783.
[19] Castilla MA, Moreno-Bueno G, Romero-Perez L, et al. Micro-RNA signature of the epithelial-mesenchymal transition in endometrial carcinosarcoma. J Pathol, 2011,223:72–80.
[20] Wellner U, Schubert J, Burk UC, et al. The EMT-activator ZEB1 promotes tumorigenicity by repressing stemness-inhibiting microRNAs. Nat Cell Biol, 2009,11:1487–1496.
[21] Reinhold WC, Reimers MA, Maunakea AK, et al. Detailed DNA methylation profiles of the E-cadherin promoter in the NC1-60 cancer cells. Mol Cancer Ther, 2007,6:391–403.
[22] Zhang Z, Zhang B, Li W, et al. Epigenetic Silencing of miR-203 Upregulates SNAI2 and Contributes to the Invasiveness of Malignant Breast Cancer Cells. Genes Cancer, 2011,2:782–791.
[23] Tellez CS, Juri DE, Do K, et al. EMT and stem cell-like properties associated with miR-205 and miR-200 epigenetic silencing are early manifestations during carcinogen-induced transformation of human lung epithelial cells. Cancer Res, 2011,71:3087–3097.
[24] Wiklund ED, Bramsen JB, Hult T, et al. Coordinated epigenetic repression of the miR-200 family and miR-205 in invasive bladder cancer. Int J Cancer, 2011,128:1327–1334.
[25] Vrba L, Jensen TJ, Garbe JC, et al. Role for DNA methylation in the regulation of miR-200c and miR-141 expression in normal and cancer cells. PLoS One, 2010,5:e8697.
[26] Gregory PA, Bracken CP, Smith E, et al. An autocrine TGF-beta/ ZEB/miR-200c signaling network regulates establishment and maintenance of epithelial-mesenchymal transition. Mol Biol Cell, 2011,22:1686–1698.
[27] Kim NH, Kim HS, Li XY, et al. A p53/miRNA-34 axis regulates Snail1-dependent cancer cell epithelial-mesenchymal transition. J Cell Biol, 2011,195:417–433.
[28] Kumaswamy R, Muduluuru G, Ceppi P, et al. MicroRNA-30a inhibits epithelial-to-mesenchymal transition by targeting Snai1 and is downregulated in non-small cell lung cancer. Int J Cancer, 2012,130:2044–2053.
[29] Siemens H, Jackstadt R, Hunten S, et al. miR-34 and SNAIL form a double-negative feedback loop to regulate epithelial-mesenchymal transitions. Cell Cycle, 2011,10:4256–4271.
[30] Chang CJ, Chao CH, Xia W, et al. p53 regulates epithelial-mesenchymal transition and stem cell properties through modulating microRNAs. Nat Cell Biol, 2011,13:317–323.
[31] Kim T, Veronese A, Pichiorri F, et al. p53 regulates epithelial-mesenchymal transition through microRNAs targeting ZEB1 and ZEB2. J Exp Med, 2011,208:875–883.
Tao ZH, Wan JL, Zeng LY, et al. miR-612 suppresses the invasive-metastatic cascade in hepatocellular carcinoma. J Exp Med, 2013, 210:789–803.

Mani SA, Guo W, Liao MJ, et al. The epithelial-mesenchymal transition generates cells with properties of stem cells. Cell, 2008, 133:704–715.

Morel AP, Lievre M, Thomas C, et al. Generation of breast cancer stem cells through epithelial-mesenchymal transition. PLoS One, 2008, 3:e2888.

Shimono Y, Zabala M, Cho RW, et al. Downregulation of miRNA-200c links breast cancer stem cells with normal stem cells. Cell, 2009, 138:592–603.

Ma L, Young J, Prabhala H, et al. miR-92a promotes lymph node metastasis of human esophageal squamous cell carcinoma via E-cadherin. J Biol Chem, 2011, 286:10725–10734.

Martello G, Rosato A, Ferrari F, et al. A microRNA targeting dicer for metastasis control. Cell, 2010, 141:1196–1207.

Chen ZL, Zhao XH, Wang JW, et al. microRNA-181a expression to promote breast cancer metastasis. Nature, 2007, 451:147–152.

Taylor MA, Mossey-Alaoui K, Thompson CL, et al. TGFBeta up-regulates miR-181a expression to promote breast cancer metastasis. J Clin Invest, 2013, 123:150–163.

Xia H, Ooi LL, Hui KM. miR-216a/217 induces epithelial-mesenchymal transition in breast cancer. Sci Signal, 2011, 4:pi5.

Kong W, Yang H, He L, et al. MicroRNA-155 is regulated by the transforming growth factor beta2/Smad pathway and contributes to epithelial cell plasticity by targeting RhoA. Mol Cell Biol, 2008, 28:6773–6784.

Nicoloso MS, Spizzo R, Shimizu M, et al. MicroRNAs—the micro steering wheel of tumour metastases. Nat Rev Cancer, 2009, 9:293–302.

Valastyan S, Reinhardt F, Benaich N, et al. A pleiotropically acting microRNA, miR-31, inhibits breast cancer metastasis. Cell, 2009, 137:1028–1046.

Tavaozie SF, Alarcon C, Oskarsson T, et al. Endogenous human microRNAs that suppress breast cancer metastasis. Nature, 2008, 451:147–152.

Zhang Y, Yang P, Sun T, et al. miR-126 and miR-126* repress recruitment of mesenchymal stem cells and inflammatory monocytes to inhibit breast cancer metastasis. Nat Cell Biol, 2013, 15:284–294.

Barth D, Malhotra R, Ravi B, et al. MicroRNA let-7: an emerging next-generation cancer therapeutic. Curr Oncol, 2010, 17:70–80.

Lee YS, Dutta A. The tumor suppressor microRNA let-7 represses the HMGA2 oncogene. Genes Dev, 2007, 21:1025–1030.

Johnson SM, Grosshans H, Shingara J, et al. RAS is regulated by the let-7 microRNA family. Cell, 2005, 120:635–647.

Mayr C, Hemann MT, Bartel DP. Disrupting the pairing between let-7 and Hmga2 enhances oncogenic transformation. Science, 2007, 315:1576–1579.

Di Leva G, Piovano C, Gasparini P, et al. Estrogen mediated-activation of miR-191/425 cluster modulates tumorigenicity of breast cancer cells depending on estrogen receptor status. PLoS Genet, 2013, 9:e1003311.

Kuo PL, Liao SH, Hung JY, et al. MicroRNA-33a functions as a bone metastasis suppressor in lung cancer by targeting parathyroid hormone related protein. Biochim Biophys Acta, 2013, 1830:3756–3766.

Zhu S, Wu H, Wu F, et al. MicroRNA-21 targets tumor suppressor genes in invasion and metastasis. Cell Res, 2008, 18:350–359.

Asangani IA, Rasheed SA, Nikolova DA, et al. MicroRNA-21 (miR-21) post-transcriptionally downregulates tumor suppressor Pdcdf and stimulates invasion, intravasation and metastasis in colorectal cancer. Oncogene, 2008, 27:2128–2136.

Lou Y, Yang X, Wang F, et al. MicroRNA-21 promotes the cell proliferation, invasion and migration abilities in ovarian epithelial carcinomas through inhibiting the expression of PTEN protein. Int J Mol Med, 2010, 26:819–827.

Cottonham CL, Kaneko S, Xu L. miR-21 and miR-31 converge on TIAM1 to regulate migration and invasion of colon carcinoma cells. J Biol Chem, 2010, 285:35293–35302.

Liu M, Tang Q, Qiu M, et al. miR-21 targets the tumor suppressor RhoB and regulates proliferation, invasion and apoptosis in colorectal cancer cells. FEBS Lett, 2011, 585:2998–3005.

Ma L, Teruya-Feldstein J, Weinberg RA. Tumour invasion and metastasis initiated by microRNA-10b in breast cancer. Nature, 2007, 449:682–688.

Sasayama T, Nishihara M, Kondoh T, et al. MicroRNA-10b is overexpressed in malignant glioma and associated with tumor invasive factors, uPAR and RhoC. Int J Cancer, 2009, 125:1407–1413.

Li QJ, Zhou L, Yang F, et al. MicroRNA-10b promotes migration and invasion through CADM1 in human hepatocellular carcinoma cells. Tumour Biol, 2012, 33:1455–1465.

Tian Y, Luo A, Cai Y, et al. MicroRNA-10b promotes migration and invasion through KLF4 in human esophageal cancer cell lines. J Biol Chem, 2010, 285:7986–7994.

Weiss FU, Marques IJ, Woltering JM, et al. Retinoic acid receptor antagonists inhibit miR-10a expression and block metastatic behavior of pancreatic cancer. Gastroenterology, 2009, 137:2136–2145.

Huang Q, Gumireddy K, Schrier M, et al. The microRNAs miR-373 and miR-520c promote tumor invasion and metastasis. Nat Cell Biol, 2008, 10:202–210.

Liu P, Wilson MJ. miR-520c and miR-373 upregulate MMP9 expression by targeting mTOR and SIRT1, and activate the Ras/Raf/MEK/Erk signaling pathway and NF-kappaB factor in human fibrosarcoma cells. J Cell Physiol, 2012, 227:867–876.

Korpal M, Ell BJ, Buffa FM, et al. Direct targeting of Sec23a by miR-21 (miR-21) post-transcriptionally downregulates tumor suppressor Pdcdf and stimulates invasion, intravasation and metastasis in colorectal cancer. Oncogene, 2008, 27:2128–2136.

Trang P, Medina PP, Wiggins JF, et al. Direct targeting of Sec23a by miR-21 (miR-21) post-transcriptionally downregulates tumor suppressor Pdcdf and stimulates invasion, intravasation and metastasis in colorectal cancer. Oncogene, 2008, 27:2128–2136.

Esquela-Kerscher A, Trang P, Wiggins JF, et al. The let-7 microRNA reduces tumor growth in mouse models of lung cancer.
Xu X, Fan Z, Kang L, et al. Hepatitis B virus X protein represses prostate cancer stem cells and metastasis by directly repressing CD44. Nat Med, 2011, 17:211–215.

[70] Wiggins JF, Ruffino L, Kelnar K, et al. Development of a lung cancer therapeutic based on the tumor suppressor microRNA-34. Cancer Res, 2010, 70:5923–5930.

[71] Ma L, Reinhardt F, Pan E, et al. Therapeutic silencing of miR-10b inhibits metastasis in a mouse mammary tumor model. Nat Biotechnol, 2010, 28:341–347.

[72] Wang FE, Zhang C, Maminishkis A, et al. MicroRNA-204/211 alters epithelial physiology. FASEB J, 2010, 24:1552–1571.

[73] Liu YN, Yin JJ, Abou-Kheir W, et al. MiR-1 and miR-200 inhibit EMT via Slug-dependent and tumorigenesis via Slug-independent mechanisms. Oncogene, 2013, 32:296–306.

[74] Xu Q, Sun Q, Zhang J, et al. Downregulation of miR-153 contributes to epithelial-mesenchymal transition and tumor metastasis in human epithelial cancer. Carcinogenesis, 2013, 34:539–549.

[75] Liang YJ, Wang QY, Zhou CX, et al. MiR-124 targets Slug to regulate epithelial-mesenchymal transition and metastasis of breast cancer. Carcinogenesis, 2013, 34:713–722.

[76] Zhang Z, Liu S, Shi R, et al. MiR-27 promotes human gastric cancer cell metastasis by inducing epithelial-to-mesenchymal transition. Cancer Genet, 2011, 204:486–491.

[77] Hamada S, Satoh K, Miura S, et al. MiR-197 induces epithelial-mesenchymal transition in pancreatic cancer cells by targeting p120 catenin. J Cell Physiol, 2013, 228:1255–1263.

[78] Zhang LY, Liu M, Li X, et al. MiR-490-3p modulates cell growth and epithelial to mesenchymal transition of hepatocellular carcinoma cells by targeting endoplasmic reticulum-Golgi intermediate compartment protein 3 (ERGIC3). J Biol Chem, 2013, 288:4035–4047.

[79] Rice SJ, Lai SC, Wood LW, et al. MicroRNA-33a mediates the regulation of high mobility group AT-hook 2 gene (HMGA2) by thyroid transcription factor 1 (TTF-1/NKX2-1). J Biol Chem, 2013, 288:16348–16360.

[80] Sun Q, Zhang J, Cao W, et al. Dysregulated miR-363 affects head and neck cancer invasion and metastasis by targeting podoplanin. Int J Biochem Cell Biol, 2013, 45:513–520.

[81] Yamasaki T, Seki N, Yoshino H, et al. microRNA-216 inhibits cell migration and invasion in renal cell carcinoma through targeting caveolin-2 involved in focal adhesion pathway. J Urol, 2013, 190:1059–1068.

[82] Chou J, Lin JH, Brenot A, et al. GATA3 suppresses metastasis and modulates the tumor microenvironment by regulating microRNA-29b expression. Nat Cell Biol, 2013, 15:201–213.

[83] Ding J, Huang S, Wang Y, et al. Genome-wide screening revealed that miR-195 targets the TNF-alpha/NF-kappaB pathway by downregulating IKKalpha and TAB3 in hepatocellular carcinoma. HEPATOLOGY, 2013, 58:205–217.

[84] Xu X, Fan Z, Kang L, et al. Hepatitis B virus X protein represses miRNA-148a to enhance tumorogenesis. J Clin Invest, 2013, 123:630–645.

[85] Goldberger N, Walker RC, Kim CH, et al. Inherited variation in miR-290 expression suppresses breast cancer progression by targeting the metastasis susceptibility gene arid4b. Cancer Res, 2013, 73:2671–2681.

[86] Liang L, Li X, Zhang X, et al. MicroRNA-137, an HMGA1 target, suppresses colorectal cancer cell invasion and metastasis in mice by directly targeting FML1. Gastroenterology, 2013, 144:624–635.

[87] Yeh YM, Chuang CM, Chao KC, et al. MicroRNA-138 suppresses ovarian cancer cell invasion and metastasis by targeting SOX4 and HIF-1alpha. Int J Cancer, 2013, 133:867–878.

[88] Yang H, Fang F, Chang R, et al. MicroRNA-140-5p suppresses tumor growth and metastasis by targeting TGFBR1 and FGFR9 in hepatocellular carcinoma. Hepatology, 2013, 58:205–217.

[89] Noguchi S, Mori T, Hoshino Y, et al. MicroRNA-143 functions as a tumor suppressor in human bladder cancer T24 cells. Cancer Lett, 2011, 307:211–220.

[90] Ni Y, Meng L, Wang L, et al. MicroRNA-143 functions as a tumor suppressor in human esophageal squamous cell carcinoma. Gene, 2013, 517:197–204.

[91] Ibaheiwy RA, Ward TM, Dykochoom DM, et al. The microRNA-23b/-27b cluster suppresses the metastatic phenotype of castration-resistant prostate cancer cells. PLoS One, 2012, 7:e52106.

[92] Okuda H, Xing F, Pandey PR, et al. miR-7 suppresses brain metastasis of breast cancer stem-like cells by modulating KLF4. Cancer Res, 2013, 73:1434–1444.

[93] Yu L, Li J, Zhang B, et al. miR-26a inhibits invasion and metastasis of nasopharyngeal cancer by targeting EZH2. Oncol Lett, 2013, 5:1223–1228.

[94] Liu N, Tang LL, Sun Y, et al. MiR-29c suppresses invasion and metastasis by targeting TIA1 in nasopharyngeal carcinoma. Cancer Lett, 2013, 329:181–188.

[95] Zhong M, Bian Z, Wu Z. miR-30a suppresses cell migration and invasion through downregulation of PIK3CD in colorectal carcinoma. Cell Physiol Biochem, 2013, 31:209–218.

[96] Dynoodt P, Speeckaert R, De Wever O, et al. miR-145 overexpression suppresses the migration and invasion of metastatic melanoma cells. Int J Oncol, 2013, 42:1443–1451.

[97] Yang X, Zhang J, Huang X, et al. miR-145 suppresses cell invasion in hepatocellular carcinoma cells: miR-145 targets ADAM17. Hepatol Res, 2013 Apr 28. [Epub ahead of print]

[98] Zhao G, Zhang JG, Liu Y, et al. MiR-148b functions as a tumor suppressor in pancreatic cancer by targeting AMPKalpha1. Mol Cancer Ther, 2013, 12:83–93.

[99] Wu X, Liu T, Fang O, et al. miR-15a/b-2 cluster suppresses the metastatic phenotype of castration-resistant prostate cancer cells. PLoS One, 2012, 7:e52106.

[100] Yu YH, Chen HA, Chen PS, et al. MiR-520h-mediated FOXC2 regulation is critical for inhibition of lung cancer progression by resveratrol. Oncogene, 2013, 32:431–443.

[101] Li B, Song Y, Liu TJ, et al. miRNA-22 suppresses colon cancer cell migration and invasion by inhibiting the expression of T-cell lymphoma invasion and metastasis 1 and matrix metalloproteinases 2 and 9. Oncol Rep, 2012, 29:1932–1938.

[102] Xu C, Zeng Q, Xu W, et al. miRNA-100 inhibits human bladder urothelial carcinogenesis by directly targeting mTOR. Mol Cancer Ther, 2013, 12:207–219.

[103] Kliese N, Gobrecht P, Pachow D, et al. MicroRNA-2013:73:2671-2681.
miRNAs in cancer metastasis

Res, 2013;11:182–193.

[105] Iino I, Kikuchi H, Miyazaki S, et al. Effect of miR-122 and its target gene cationic amino acid transporter 1 on colorectal liver metastasis. Cancer Sci, 2013;104:624–630.

[106] Pencheva N, Tran H, Buss C, et al. Convergent multi-miRNA targeting of ApoE drives LRP1/LRP8-dependent melanoma metastasis and angiogenesis. Cell, 2012;151:1068–1082.

[107] Tian Q, Liang L, Ding J, et al. MicroRNA-550a acts as a pro-metastatic gene and directly targets cytoplasmic polyadenylation element-binding protein 4 in hepatocellular carcinoma. PLoS One, 2012;7:e48958.

[108] Du WW, Fang L, Li M, et al. MicroRNA miR-24 enhances tumor invasion and metastasis by targeting PTPN9 and PTPRF to promote EGF signaling. J Cell Sci, 2013;126:1440–1453.

[109] Fang L, Du WW, Yang W, et al. miR-93 enhances angiogenesis and metastasis by targeting LATS2. Cell Cycle, 2012;11:4352–4365.