Published in final edited form as:
Biochim Biophys Acta. 2014 April ; 1845(2): 255–265. doi:10.1016/j.bbcan.2014.02.002.

Regulation of microRNAs in Cancer Metastasis

Juliette M.C. Bouyssou[1,2], **Salomon Manier**[1], **Daisy Huynh**[1], **Samar Issa**[2], **Aldo M. Roccaro**[1], and **Irene M. Ghobrial**[1]

[1]Dana-Farber Cancer Institute, Department of Medical Oncology, Harvard Medical School, 450 Brookline Avenue, HIM 246, Boston, MA 02215, USA

[2]Ecole de Biologie Industrielle, 32 Boulevard du port, 95094, Cergy-Pontoise cedex, France

Abstract

Metastasis is a phenomenon of crucial importance in defining prognosis in patients with cancer and is often responsible for cancer-related mortality. It is known that several steps are necessary for clonal cells to disseminate from their primary tumor site and colonize distant tissues, thus originating metastatic lesions. Therefore, investigating the molecular actors regulating this process may provide helpful insights in the development of efficient therapeutic responses. Recent evidences have indicated the role of microRNAs (miRNAs) in modulating the metastatic process in solid tumors. miRNAs are small regulatory non-coding RNAs that bind specific target mRNAs, leading to translational repression. miRNAs are known to act as negative regulators of gene expression and are involved in the regulation of biological processes, including cell growth, differentiation and apoptosis, both in physiological conditions and during diseases, such as tumors. In the specific field of tumorigenesis, miRNAs play an important role in mediating oncogenesis and favoring tumor progression, as a result of their ability to modulate epithelial-to-mesenchymal transition (EMT) and other series of events facilitating the formation of metastasis. The role of miRNAs in cancer development has been widely studied and has helped elucidate events such as the change in expression of oncogenes, tumor-suppressors and cancer-related proteins. This review focuses on the mechanisms underlying the role of miRNAs as part of the metastatic process.

Keywords

microRNAs; cancer; metastasis; EMT; epigenetics

Corresponding Author: Irene M. Ghobrial, MD, Dana-Farber Cancer Institute, Boston, MA 02115, Phone: 617-632-4198, Fax: 617-582-8608, Irene_ghobrial@dfci.harvard.edu.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

Introduction

Metastasis is largely implicated in cancer aggressiveness and outcome. Statistics point out that it is responsible for more than 90% of mortality as documented in patients with solid tumors[1]. It is therefore important to understand the signaling networks regulating this phenomenon[1]. Metastasis is a complex multi-step event leading to the formation of new tumoral sites arising from a primary tumor[2,3]. The metastatic process is initiated by the dissemination of clonal cells from the primary tumor site that invade the extracellular matrix and the surrounding stroma[4]. The process of epithelial-mesenchymal transition (EMT) is known to play a role in this step of metastasis formation[5]. The metastatic clones must survive anoikis, an immune reaction triggered by the loss of interaction between the cells and the extracellular matrix[6]. Intravasation into the lumen of a lymphatic or blood vessel allows the tumor circulating cells (CTCs) to reach distant organs. Metastasis is a low probability event and specific conditions in the host tissue are necessary for initiation of a new tumoral site[7]. The ‘’seed and soil” hypothesis states that the nature of the host environment where cells will metastasize is as important as the nature of the tumor from which the cell originates. It also underlines the importance of the interactions between tumor and supportive stroma[4]. The premetastatic niches are conditioned by oncogenic factors such as proteins and microRNAs that can notably be transported from the primary tumor via exosomes[8].

MicroRNAs (miRNAs) are small, endogenous, evolutionarily conserved non-coding ribonucleotidic acids. Their length usually ranges from 19 to 22 nucleotides. It is estimated that up to 3% of the human genome codes for miRNA sequences[9]. miRNAs are processed in the nucleus and the cytoplasm by a specific machinery and mature miRNAs are part of the RNA-induced silencing complex (RISC) which enables post-transcriptional control of gene expression. They bind to complementary sequences in the 3’ untranslated regions (3’UTR) of their target messenger RNAs (mRNAs). If there is perfect complementarity, the cleavage of the target mRNA is induced. If the complementarity is only partial, the binding of miRNAs leads to translational repression by inhibiting translation into proteins of the sequence[10]. Furthermore, it was shown that miRNAs can target not only mRNAs, but also DNA and proteins[11].

miRNAs are involved in many molecular pathways and in pivotal biological processes including cell growth, development, differentiation, proliferation and cell death[12]. Importantly, recent evidences have demonstrated the role of miRNAs in modulating the metastatic process in the context of solid tumors[13,14]. Among the first metastatic promoter miRs to be discovered was miR-10b, identified while screening upregulated miRs in breast cancer. *In vivo* functional studies demonstrated that overexpression of miR-10b triggered tumor invasion and distant metastasis in otherwise non-metastatic breast tumors[15]. Another study identified metastasis-suppressor miRNAs. They identified three miRNAs (miR-335, miR-126, and miR-206) that suppress metastasis [16]. miR-335 and miR-206 were shown to suppress invasion, while miR-126 was subsequently shown to suppress metastatic angiogenesis[17]. Invasion enables the cells to evade the primary tumor by breaching the basement membrane, enter the surrounding ECM and stroma and invade new tissues after intravasation while angiogenesis is a series of events leading to

neovascularization, thus supporting tumor growth and providing tumoral cells with access to systemic circulation[18]. As underlined by these initial discoveries, these two processes are key features of successful metastasis formation.

The study of these metastasis promoter miRNAs and metastasis suppressor miRNAs therefore represents a new approach that may enhance our understanding of the molecular mechanisms modulating the metastatic cascade.

The present review looks into the factors that may induce an imbalance of miRNA expression in tumor cells, thus facilitating the metastatic process.

miRNA processing machinery and metastasis

After the transcription of the miRNA-coding DNA sequences by RNA polymerase II, the primary miRNA (pri-miRNA) is processed in the nucleus into a precursor miRNA (pre-miRNA)consisting in a stem-loop structure of about 70 nucleotides by the RNase III endonuclease Drosha[19]. Drosha is part of the microprocessor complex along with the co-factor DGCR8, a double stranded RNA-binding domain (dsRBD) protein, known as Pasha. The two RNAse domains of Drosha enable the degradation of the pri-miRNA into pre-miRNA by cleaving the 5’ and 3’ ends of the pri-miRNA[20].The intermediate pre-miRNA is actively transported to the cytoplasm by the coordinate action of Exportin-5 and Ran-GTP[21]. Once in the cytoplasm, the RNase III nuclease Dicer1 carries out the maturation of the pre-miRNA into a final 22 nucleotide-long double-stranded RNA. The latter reaction is often accompanied with the formation of RISC (RNA-induced silencing complex), which enables silencing of mRNAs. The RISC complex is made up of a strand of the mature miRNA called guide strand as well as Dicer, TRBP(TAR RNA binding protein), PACT (protein activator of PKR) and Argonaute proteins[10]. Partners of Dicer and the RISC complex, such as EIF2C1–4 (Argonaute-1–4-like proteins), the DEAD box RNA helicase Gemin3–4, HSPCA (Hsp90) and PACT are also part of the miRNA machinery[22]. It has been observed that in cancer cells, the global levels of miRNAs are decreased[23,24]. A relevant study showed that a general decrease in miRNAs caused by knockdown of Dicer and Drosha promoted tumorigenesis[25]. In the same way, there is evidence that Dicer1 functions as a haploinsufficient tumor suppressor[26]. Therefore, the impact of Dicer and the other components of the miRNA processing complex have been investigated in the specific case of metastasis, and some deregulations have been shown.

miR-221/222 is a well-known miR cluster that has been shown to influence cancer metastasis by positively regulating tumor growth, invasion and EMT in breast cancer[27–30], lung cancer[31], liver cancer[31], pancreatic[32] and colorectal cancer[33]. Nucleolin (NCL) is a nucleolar protein and a component of the Drosha/DGCR8 microprocessor complex[34]. Interestingly, it was demonstrated that NCL promotes maturation of a set of metastasis promoter miRs, such as the miR221/222 cluster[34] but also miR-21, miR-103[34] and miR-15a/16[35]. Furthermore, levels of these miRs correlated in breast cancer with NCL. Importantly, NCL targeting led to a decrease of the NCL-dependent miRs and an inhibition of breast cancer cell aggressiveness *in vitro* and *in vivo*[34].

The role of the miRNA family miR103/107 has been recently studied[36]. Authors have demonstrated that this family targeted Dicer, leading to a reduction of miRNA biogenesis and caused a downregulation of miR-200 levels, thus inducing EMT. High levels of miR-103/107 in human breast cancer cells correlated with metastasis and poor outcome. The role of miR-107 was also found to be correlated with gastric cancer metastasis[37] and consistently with Martello's previous study[36], Dicer was identified as a direct target of miR-107. Interestingly, upregulation of Dicer led to the same consequences as silencing of miR-107, namely significant decrease of *in vitro* migration and invasion and *in vivo* liver metastasis of nude mice. Moreover, restoration of Dicer expression impaired miR-107-induced gastric cancer cell invasion and metastasis. Therefore Dicer has been proven to act as a suppressor of metastasis in gastric cancer cells.

Dicer can also be targeted by TAp63, which is part of the p53 family[38]. A direct transcriptional regulation occurs through interaction between TAp63 and the Dicer promoter, enabling suppression of metastasis through a coordinate regulation of the miRNA miR-130b and Dicer. In metastatic mice and TAp63 deficient cells, low levels of Dicer were assessed and the metastatic potential of these cells was significantly impacted by modulating expression of miR-103b and Dicer. Similarly, p53, p63 and p73 function as both positive and negative regulators of miRNA processing components such as Dicer, TRBP2, Drosha, DGCR8, and Argonaute proteins, and therefore play a role in the regulation of tumorigenesis, EMT and metastasis[39]. A significant correlation was established between the expression of several Argonaute proteins, EIF2C2, EIF2C3, EIF2C4 and PIWIL4 and the presence of distant metastasis in colon cancer cells. Dicer mRNA levels in breast cancer cells prove to have an independent prognostic impact in metastasis[40]. In breast cancer cell lines, Dicer expression was lower in cells displaying a mesenchymal phenotype than those displaying an epithelial phenotype. The same observation was made in metastatic subpopulations derived from a breast cancer cell line[40]. These evidences further confirmed the role of decreased Dicer expression in tumor cells and their enhanced EMT.

However, the role of Dicer in metastasis remains uncertain as some studies contradict the previously described findings and show a correlation between metastasis and an increased expression of Dicer and other components of the miRNA processing machinery. Indeed, recent studies have demonstrated higher Dicer expression in melanoma cells compared to melanocytic nevi, a form of benign neoplasm[41]. Dicer overexpression in patients with cutaneous melanoma positively correlated with tumor growth, invasion and metastasis. Furthermore, Dicer, Drosha and Gemin4, three proteins involved in miRNA biogenesis, were found to be upregulated in invasive melanoma versus melanoma *in situ*. Moreover, an overexpression of major components of the miRNA biogenesis complex, including Dicer and its partners EIF2C1, EIF2C2, Exportin 5, HSPCA, TNRC6B (trinucleotide repeat containing 6) and MOV10, a putative RNA helicase and component of the RISC were discovered in metastatic prostate adenocarcinoma[22]. In the first study, Dicer expression was also assessed in two other cutaneous malignancies, carcinoma and sarcoma but only melanoma featured upregulation of this enzyme. Interestingly, MITF (Microphthalmia-Associated Transcription Factor) is a transcriptional regulator specific of melanocytes and also a direct transcriptional target of Dicer. Targeted knock out of Dicer is lethal to

melanocytes[42]. These findings display evidence that Dicer plays a crucial role in the function of this type of cells and may account for this specific dysregulation. In prostate adenocarcinoma, the increased level of Dicer and its partners can be explained by the overexpression of a large number of miRNAs differentially expressed in this type of cancer[43,44].

Other epigenetic regulations of miRNAs

ADAR editing, mediated by adenosine deaminase acting on RNA process occurs in regions of double-stranded RNAs and results in the replacement of the adenosine by inosine. This phenomenon has been found to occur for some miRNAs[45]. It is thus assumed that this editing can impact miRNA regulation. In a recent study by Mobley et al.[46], ADAR1, an enzyme involved in ADAR editing was found to be regulated by the transcription factor CREB (cAMP Response Element-Binding protein) in highly metastatic melanoma cell lines. The correlation between the decrease of ADAR1 expression and melanoma progression suggests that altered editing can contribute to metastasis in melanoma cells.

Some tumor-suppressor genes (TSG) are significantly hypermethylated in cancer. Consequently, the possibility of a hypermethylation of tumor suppressor miRNAs has also been investigated. Epigenetic silencing due to this phenomenon has been described for numerous cancer-related miRNAs. To assess a possible role of this epigenetic regulation in metastatic progression, recent studies have evaluated miRNA expression profiling in metastatic cell lines exposed to the DNA demethylating agent 5-aza-2’-deoxycytidine. This led to the discovery of 5 miRNAs with cancer-specific methylation: miR-148a, miR-9-1, 2 and 3 as well as the miR-34b/c cluster. For two of these miRNAs, miR-148a and the miR34b/c cluster, restoration of expression affected *in vitro* and *in vivo* invasiveness of the cells. Moreover, epigenetic silencing of these miRNAs led to the activation of E3F3, c-MYC and CDK6 (Cyclin-Dependent Kinase 6) for miR34b/c and TGIF2 (TGFB-induced factor homeobox 2) for miR48a, which are oncogenic and metastatic genes. An upregulation of these oncogenes was correlated with miR34b/c methylation in human primary tumors. Interestingly, the primary tumors that gave rise to metastasis displayed a significantly higher methylation level for these miRNAs. Downregulation of miR-203 in metastatic breast cancer cells, caused by hypermethylation of its promoter, leads to the regulation of its metastasis promoting target SNAI2 (a member of the Snail family of zinc-finger transcription factors) and to an increased cell invasion and migration *in vitro*[47]. In the same way, downregulation of miR-212 is due to both promoter hypermethylation and loss of heterozygosity. miR-212 targets manganese superoxide dismutase (MnSOD) to inhibit EMT and its overexpression inhibited cell migration and invasion *in vitro* and formation of intrahepatic and pulmonary metastasis *in vivo* in colorectal cancer[48]. A study has also identified seven miRNAs in the imprinted DLK1-DIO3 region (miRs-300, 382, 494, 495, 539, 543, and 544) that function cooperatively to repress EMT as well as proliferation of carcinoma cells. Silencing of the cluster, which occurs via hypermethylation of upstream CpG islands in human ductal carcinomas, confers morphological, molecular, and function changes consistent with an EMT[49]. miR-124 inhibits cell proliferation, invasion and metastasis in pancreatic cancer and mir-124 genes are highly methylated in pancreatic cancer tissues compared with non-cancerous tissues. Hypermethylation mediates the

silencing of miR-124, promoting metastasis formation[50,51]. In contrast, miR-135b, promoting metastasis *in vivo* in non-small-cell lung cancer cells (NSCLC), is dually regulated by DNA demethylation and NFκB signaling[52]. Finally, epigenetic activation of the miR-200 family by the protein complex hnRNP U/PCAF/RNAPol II that increases histone acetylation contributes to H19-mediated metastasis suppression in hepatocellular carcinoma[53].

miRNAs and metastasis

miRNAs have been reported to directly regulate the metastatic process both *in vitro* and *in vivo* (Table 1). Among those, miR-21 has been described as upregulated in many types of cancer[43,54–56] and is involved in all the steps of cancer progression, including tumorigenesis and metastasis[55,57–59].

A correlation between miR-21 and lymph node metastasis was demonstrated in gastric cancer[60,61], breast cancer[62–64], ovarian carcinoma[65], liver fluke-associated cholangiocarcinoma[66], pulmonary neuroendocrine tumor[67] but also more generally in metastatic types of cancer such as colon, bladder and lung cancers[62]. A correlation with distal metastasis as well as a promoting effect on metastasis formation through the regulation of the tumor suppressor PTEN was also shown in NSCLCs[68,69] and with venous invasion and liver metastasis in colorectal cancer[68,70].

Interestingly, the action of miR-21 on metastasis seems to occur through the regulation of multiple targets, the most commonly reported being PTEN[56,61,65,68,69,71–73]. miR-21 promotion of metastasis occurs through the regulation of the guanidine exchange factor of the Rac GTPase TIAM1 concomitantly with miR-31 in colon carcinoma[74], of the tumor suppressors PTEN and Pdcd4 as well as the anti-proliferative protein BTG2 in melanoma[71] and of the tumor suppressor RHOB in hepatocellular carcinoma and breast cancer[75]. Importantly, miR-21 has been reported to modulate invasion, intravasation and metastasis in colorectal cancer[76] and invasion and metastasis in breast cancer[77], due to modulation of Pdcd4.

In breast cancer, HER2/neu signaling upregulates miR-21 via the MAPK (ERK1/2) pathway, enhancing tumor metastasis[78] while interestingly, in another study miR-21 was shown as activating AKT and ERK1/2 signaling pathways through the targeting of PTEN in prostate cancer cells, thereby enhancing HIF-1α and VEGF expression and promoting angiogenesis[79]. Supporting the second study, antagonism of miR-21 was shown to inactivate the AKT and ERK1/2 pathways through targeting PTEN, thus reversing EMT and cancer stem cell phenotype[72].

Regulation of miR-21 also plays a role in potential treatments targeting metastasis. Indeed, resveratrol is a molecule exerting metastasis suppressive effects through reduced pAkt and miR-21 levels and the resulting elevated expression of its tumor suppressor target Pdcd4[80]. In the same way, miR-21 inhibition and subsequent increase in Pdcd4 levels caused by curcumin inhibited tumor growth, invasion and *in vivo* metastasis in a chicken-embryo-metastasis assay[81]. Finally, miR-21 has also been linked to both metastasis and resistance in certain cases such as in breast cancer for which therapeutic resistance occurs

via NF-κB-dependent miR-21 induction[73] or in NSCLC in which it induces chemo or radio-resistance[69].

The let-7 miRNA family consists of twelve members and is famous for its role in stem cell differentiation and normal development and for its tumor suppressor activity[82]. The RNA-binding protein LIN28 is a key developmental regulator and represses let-7 biogenesis, thus regulating its activity[83]. Besides their role in tumor formation, members of the let-7 family have also shown an effect on metastasis.

The metastasis suppressing effect of the let-7 miRs happens through the regulation of various targets. A study demonstrated that the repression of the let-7 family members' biogenesis by LIN28 promotes colon cancer *in vivo*[84]. The repression of LIN28 by Raf kinase inhibitory protein (RKIP) leads to an increase in let-7 levels and subsequent repression of the protein HMGA2, a chromatin remodelling protein that activates pro-invasive and pro-metastatic genes including SNAIL, resulting in the suppression of bone metastasis in a breast cancer *in vivo* model[85]. In addition, the metastasis suppresive effect of let-7 in breast cancer, allegedly occurs through targeting of HMGA2 and the oncogene HRAS[86]. More specifically, let-7g also proved to inhibit breast cancer metastasis by the regulation of two target genes, Grb2-associated binding protein 2 (GAB2) and fibronectin 1 (FN1), and consequent activation of p44/42 mitogen-activated protein kinase (MAPK) and specific matrix metalloproteinases[87]. In an *in vivo* melanoma model, let-7b inhibited Basigin, a protein involved in tumor progression and decrease metastasis[88]. Inhibition of the matrix metalloproteinase MMP11 and PBX3 by let-7c has been shown to suppress colorectal cancer metastasis *in vitro* and *in vivo*[89]. Finally, targeting of myosin IIA (MYH9) by let-7f showed inhibition of gastric cancer metastasis *in vivo*[90].

miR-9 has pivotal role in neural development in mammals amongst others[91]. It also displays a differential expression in many types of cancer but it showed opposing effects on oncogenesis[91]. For instance, miR-9 promotes the proliferation of human gastric cancer cells through targeting of CDX2 (a nuclear homeobox transcription factor)[92] while its overexpression suppresses the proliferation of ovarian carcinoma cells, partly by downregulating NFκB1[93].

mir-9-dependent effect on metastasis may vary based on the specific tumor type. For instance, miR-9 is overexpressed in breast cancer cells and directly targets CDH1, the mRNA encoding E-cadherin. miR-9-mediated inhibition of E-cadherin activates β-catenin signaling, resulting in vascular endothelial growth factor (VEGF) upregulation and consequently promotion of tumor angiogenesis. CDH1 targeting also favors EMT, endowing breast cancer cells with increased motility and invasiveness. Interestingly, MYC and MYCN activate miR-9 by binding the miR-9-3 locus. miR-9 overexpression in non metastatic breast cancer tumor cells led to the formation of pulmonary micrometastases in mice[94]. However, other studies have on the contrary, revealed an antimetastatic action for miR-9. Recent studies[95]showed that miR-9, through targeting of MMP-14, a metalloproteinase playing a critical role in metastasis and angiogenesis, regulates VEGF in neuroblastoma cells. Subsequently, miR-9 overexpression suppressed the invasion, metastasis, and angiogenesis of these cells *in vitro* and *in vivo*[95]. In uveal melanoma, miR-9 suppresses

migration and invasion of highly invasive cells by modulating the NFκB pathway, including notably the matrix metalloproteinases MMP-2 and MMP-9 and the angiogenesis-related protein VEGF-A[96]. A suppressive effect of miR-9 on metastasis was shown *in vitro* and *in vivo* in gastric cancer cells, exerted via the targeting of cyclin D1, the transcription factor Ets1 and their downstream targets of which MMP-9[97]. Finally, a study displayed evidence that Prospero homeobox 1 (PROX1), a known tumor suppressor, binds the miR-9-2 promoter and triggers its expression to suppress E-cadherin in colon cancer cells. In these cells, a correlation was established between PROX1 expression and lymph node metastasis[98].

miRNA regulation of EMT

EMT is a program involved in tissue morphogenesis during embryonic development and induced in adults for placenta formation as well as wound healing by production of fibroblasts[99]. This series of events is frequently activated in cancer cells acquiring invasive and metastatic properties[100]. During the process, epithelial cells take on features characteristic of mesenchymal cells. This results in separation, loss of polarity and adhesion and gain of motility potential. It therefore enables the cells to move to new localities and allows the progression of benign tumors into metastatic cancers[101,102].

Epithelial cells display an apico-basal polarity and are tightly associated by special junctions[100]. E-cadherin is a transmembrane protein specific of epithelial cells that plays an important role in cell-to-cell interaction[102]. Underlying interstitial spaces are filled with extracellular matrix and mesenchymal cells. The latter are non-polarized, loosely associated and highly motile cells. One of the main features of EMT is the repression of epithelial genes such as E-cadherin, resulting in loss of cell adhesion and the overexpression of mesenchymal markers like N-Cadherin and the intermediate filament protein Vimentin, leading to increased cell motility[103]. Wnt Signaling and Notch Signaling pathways are involved in EMT initiation as well as transcription factors acting via their kinase receptor such as TGFβ, FGF, EGF and PDGF[104]. The discovery of several EMT transcriptional factors has enlightened our understanding of the mechanisms underlying this process. These factors are the protein SNAIL along with the co-repressors HDAC1, HDAC3 and SIN3A, the zinc finger proteins Snail2/Slug and the EMT transcription factors ZEB1/ZEB2, the basic helix-loop-helix protein E47 and Twist. They exert a transcriptional repression of E-cadherin but some can also act as transcriptional activators in specific circumstances, inducing for instance N-cadherin expression[105]. Interestingly, they have been shown to play an important role in tumorigenesis[103]. As EMT has been related to metastasis initiation, the study of miRNAs involved in this process can offer insights into the acquisition of metastatic potential by tumoral cells. Many studies have therefore been conducted and a large number of miRNAs have been correlated with EMT[100,14,89].

Among the EMT-modulating miRNAs, the miR-200 family represents one of the most studied. It consists of miR-200a, miR-200b, miR-200c, miR-141 and miR-429. These miRs are closely linked to an epithelial cellular phenotype and have been reported as crucial regulators of EMT, thus exerting an effect on metastasis through this regulation[106].

Overexpression of miR-200b and miR-15b reversed EMT and sensitized to chemotherapy resistant tongue squamous cell carcinoma cells and suppressed metastasis *in vivo* through targeting of BMI1, a core component of the polycomb repressive complex 1 (PRC1)[107]. A correlation was also established with BMI1, E-cadherin and the inhibition of melanoma growth and metastasis *in vivo* caused by overexpression of miR-200c[108]. mir-200 proved to directly regulate E-cadherin via targeting of its transcriptional repressors ZEB1/2[106,109] and a double-negative feedback loop between ZEB1/2 and the miR-200 family regulating EMT and promoting metastasis was demonstrated[110,111]. Consistent with these findings, it was shown that overexpression of each member of the miR-200 family impaired EMT in murine mammary epithelial cells by targeting ZEB1 and ZEB2 and therefore indirectly up-regulating E-cadherin. To support these findings, the phenotype of a mouse carcinoma cell line was reversed from mesenchymal features to an epithelial phenotype by expressing ectopically the miR-200 family members[112]. In hepatocellular carcinoma, p53 represses EMT, notably by up-regulating miR-200, which leads in turn to repression of ZEB1/2[113]. In prostate adenocarcinoma, miR-1 along with mir-200 and Slug target each other in a self-reinforcing loop regulating EMT. Consequently, the overexpression of miR-1 and miR-200 inhibits EMT *in vivo*[89]. Forced expression of miR-200 inhibited EMT, invasion and metastasis of lung adenocarcinoma cells[114] and it was also shown that targeting of Flt1/VEGFR1 had anti-metastatic effects in this type of cancer[115]. A correlation was demonstrated between miR-200c and liver metastasis of colon cancer cells[116].

In spite of all these studies reporting a metastasis suppressive action of the miR-200 family, a study demonstrated a metastasis promoting effect of miR-200s that goes beyond their regulation of E-cadherin and epithelial phenotype. Indeed, recent *in vitro* and *in vivo* evidences showed that overexpression of miR-200 in breast cancer promoted metastasis in a mouse model through direct targeting of Sec23a (involved in the COPII-mediated transport of proteins from the endoplasmatic reticulum to the Golgi apparatus), which acts on the secretion of metastasis-suppressive proteins[117].

Exosomal miRNAs and metastasis

Exosomes are 40 to 100 nanometers microvesicles derived from the intracellular endosomal compartment and released by cells in their microenvironment. Exosomes play an important role in cell-to-cell communication due to their ability to transport mRNas, miRNAs, DNA fragments and proteins from a donor cell to a recipient cell. Many types of cells can secrete exosomes, including cancer cells[118]. There is evidence that there is aberrant activity of the export machinery in cancer, causing a dysregulation in the transport of oncogenic and tumor-suppressive proteins and miRNAs. Metastasis formation relies on multiple different processes to successfully occur[119]. Therefore the cross-talk between tumor cells and other types of cells enabled by exosomes and the miRNAs they contain plays a significant role in the formation of a premetastatic niche. It was also hypothesized that exosomes can be used by cancer cells to discard tumor-suppressive miRNAs and reinforce their oncogenic properties[118].

Grange et al. demonstrated that a subset of CD-105 positive renal cell carcinoma tumor-initiating cells released exosomes that promoted angiogenesis and favored the formation of a premetastatic niche. Analysis of the tumor cell-derived exosomes' content revealed a set of proangiogenic and metastasis promoter miRNAs. Interestingly, the formation of lung metastases increased significantly in mice treated with these exosomes[120]. Similarly, a study showed that exosomes of metastatic rat adenocarcinoma cells promoted premetastatic niche formation. Furthermore, miRNA profiling of these exosomes identified a high level of expression for miR-494 and miR-542-3p, two miRNAs that target cadherin-17 and consequently cause an upregulation of matrix metalloproteinases[121]. Roccaro et al. demonstrated a transfer of exosomes from bone marrow mesenchymal stromal cells (BM-MSCs) to multiple myeloma cells. Comparison of these exosomes' content with normal BM-MSCs revealed a lower level of the tumor-suppressive miRNA miR-15a. Treatment of mice with multiple myeloma BM-MSCs-derived exosomes promoted the dissemination of the malignant cells to distant bone marrow niches[122]. In breast cancer, Tumor-associated macrophages (TAM) play an important role in promoting tumor cells' invasiveness and ability to form metastases. mir-223, a miRNA specific of TAM was detected in TAM-derived exosomes and was significantly elevated in breast cancer cells co-cultured with the latter. Treatment of the co-culture's macrophages with an antisense oligonucleotide (ASO) for miR-223 led to a decrease in breast cancer cells' invasiveness, suggesting a role for miR-223's exosome-mediated transmission[123]. A set of 15 dysregulated miRNAs which are involved in melanoma metastasis was also detected by comparing the content of melanoma cells and healthy melanocytes derived exosomes[124]. Similarly, analysis of exosomal miRNAs in a brain metastatic cell line as compared to a non-brain metastatic cell line revealed upregulation of miR-210 and downregulation of miR-19a and miR-29c[125]. Treatment of the non-metastatic cells with metastatic cell-derived exosomes induced an increase of the cells' adhesive and invasive properties.

Identification of well-known metastasis promoter miRNAs and metastasis suppressor miRNAs in tumor cell-derived exosomes suggests a potential action of these miRNAs on metastasis through exosomal transmission. Higher miR-21 levels were observed in exosomes from serum of patients with esophageal squamous cell carcinoma versus benign diseases without systemic inflammation. These levels of expression were correlated with the presence of metastasis with inflammation[126]. Exosomal miR-9, transferred from tumor cells to endothelial cells in a co-culture system, activate the JAK-STAT pathway, a signaling cascade promoting cell migration and angiogenesis[127]. When comparing the miRNA levels of a gastric cancer metastatic cell line and low metastatic cell line, an enrichment in Let-7 was observed, supporting the hypothesis that tumor cells can use exosomes to discard tumor-suppressive miRNAs[128]. Fabbri et al. uncovered another potential mechanism of action for exosomal miRNAs released by cancer cells by demonstrating that tumor-secreted miR-21 and miR-29a can reach and bind to Toll-like receptors (LTR) in surrounding immune cells, thus triggering a prometastatic inflammatory response[129].

Conclusion

miRNA expression profiles differ according to different types and stages of cancer and may provide valuable information for risk stratification and prognosis. It therefore represents an

interesting tool to predict and assess metastasis in patients with cancer. Furthermore, the use of miRNAs as therapeutics is promising and displays advantages such as the absence of off-target effects[130]. Another advantage of these molecules is that they regulate multiple targets and pathways simultaneously[131].

Nevertheless, miRNAs' action can depend on the cellular context and the stage of the metastatic process and can therefore have contradictory functions, as described in this review.

In the era of personalized medicine, miRNAs offer promising perspectives in diagnostic and therapy development for numerous diseases including cancer and metastasis. Nonetheless, there are still some challenges to address in order to use miRNAs as efficient and safe therapeutics. Identification of metastasis suppressor miRs and metastasis promoter miRs can provide valuable insights into the molecular mechanisms of metastasis and lead to the discovery of specific therapeutic agents that can be developed to prevent or delay cancer metastasis.

Acknowledgments

FINANCIAL SUPPORT

Supported in part by R01CA154648, the Leukemia and Lymphoma Society and The Multiple Myeloma Research Foundation.

REFERENCES

1. Gupta GP, Massague J. Cancer metastasis: building a framework. Cell. 2006; 127(4):679–695. [PubMed: 17110329]
2. Bracken CP, Gregory PA, Khew-Goodall Y, Goodall GJ. The role of microRNAs in metastasis and epithelial-mesenchymal transition. Cell Mol Life Sci. 2009; 66(10):1682–1699. [PubMed: 19153653]
3. Valastyan S, Weinberg RA. MicroRNAs: Crucial multi-tasking components in the complex circuitry of tumor metastasis. Cell Cycle. 2009; 8(21):3506–3512. [PubMed: 19838065]
4. Fidler IJ. The pathogenesis of cancer metastasis: the 'seed and soil' hypothesis revisited. Nat Rev Cancer. 2003; 3(6):453–458. [PubMed: 12778135]
5. Sreekumar R, Sayan BS, Mirnezami AH, Sayan AE. MicroRNA Control of Invasion and Metastasis Pathways. Front Genet. 2011; 2:58. [PubMed: 22303353]
6. Albini A, Mirisola V, Pfeffer U. Metastasis signatures: genes regulating tumor-microenvironment interactions predict metastatic behavior. Cancer Metastasis Rev. 2008; 27(1):75–83. [PubMed: 18046511]
7. Rice J. Metastasis: The rude awakening. Nature. 2012; 485(7400):S55–S57. [PubMed: 22648500]
8. Marx V. Tracking metastasis and tricking cancer. Nature. 2013; 494(7435):133–136. [PubMed: 23389545]
9. Sassen S, Miska EA, Caldas C. MicroRNA: implications for cancer. Virchows Arch. 2008; 452(1): 1–10. [PubMed: 18040713]
10. Gregory RI, Chendrimada TP, Cooch N, Shiekhattar R. Human RISC couples microRNA biogenesis and posttranscriptional gene silencing. Cell. 2005; 123(4):631–640. [PubMed: 16271387]
11. Calin GA, Croce CM. MicroRNA signatures in human cancers. Nat Rev Cancer. 2006; 6(11):857–866. [PubMed: 17060945]

12. Osada H, Takahashi T. MicroRNAs in biological processes and carcinogenesis. Carcinogenesis. 2007; 28(1):2–12. [PubMed: 17028302]
13. White NM, Fatoohi E, Metias M, Jung K, Stephan C, Yousef GM. Metastamirs: a stepping stone towards improved cancer management. Nat Rev Clin Oncol. 2011; 8(2):75–84. [PubMed: 21045789]
14. Zhang J, Ma L. MicroRNA control of epithelial-mesenchymal transition and metastasis. Cancer Metastasis Rev. 2012; 31(3–4):653–662. [PubMed: 22684369]
15. Ma L, Teruya-Feldstein J, Weinberg RA. Tumour invasion and metastasis initiated by microRNA-10b in breast cancer. Nature. 2007; 449(7163):682–688. [PubMed: 17898713]
16. Tavazoie SF, Alarcon C, Oskarsson T, Padua D, Wang Q, Bos PD, et al. Endogenous human microRNAs that suppress breast cancer metastasis. Nature. 2008; 451(7175):147–152. [PubMed: 18185580]
17. Png KJ, Halberg N, Yoshida M, Tavazoie SF. A microRNA regulon that mediates endothelial recruitment and metastasis by cancer cells. Nature. 2012; 481(7380):190–194. [PubMed: 22170610]
18. Valastyan S, Weinberg RA. Tumor metastasis: molecular insights and evolving paradigms. Cell. 2011; 147(2):275–292. [PubMed: 22000009]
19. Lee Y, Kim M, Han J, Yeom KH, Lee S, Baek SH, et al. MicroRNA genes are transcribed by RNA polymerase II. EMBO J. 2004; 23(20):4051–4060. [PubMed: 15372072]
20. Gregory RI, Yan KP, Amuthan G, Chendrimada T, Doratotaj B, Cooch N, et al. The Microprocessor complex mediates the genesis of microRNAs. Nature. 2004; 432(7014):235–240. [PubMed: 15531877]
21. Bohnsack MT, Czaplinski K, Gorlich D. Exportin 5 is a RanGTP-dependent dsRNA-binding protein that mediates nuclear export of pre-miRNAs. RNA. 2004; 10(2):185–191. [PubMed: 14730017]
22. Chiosea S, Jelezcova E, Chandran U, Acquafondata M, McHale T, Sobol RW, et al. Up-regulation of dicer, a component of the MicroRNA machinery, in prostate adenocarcinoma. Am J Pathol. 2006; 169(5):1812–1820. [PubMed: 17071602]
23. Lu J, Getz G, Miska EA, Alvarez-Saavedra E, Lamb J, Peck D, et al. MicroRNA expression profiles classify human cancers. Nature. 2005; 435(7043):834–838. [PubMed: 15944708]
24. Gaur A, Jewell DA, Liang Y, Ridzon D, Moore JH, Chen C, et al. Characterization of microRNA expression levels and their biological correlates in human cancer cell lines. Cancer Res. 2007; 67(6):2456–2468. [PubMed: 17363563]
25. Kumar MS, Lu J, Mercer KL, Golub TR, Jacks T. Impaired microRNA processing enhances cellular transformation and tumorigenesis. Nat Genet. 2007; 39(5):673–677. [PubMed: 17401365]
26. Kumar MS, Pester RE, Chen CY, Lane K, Chin C, Lu J, et al. Dicer1 functions as a haploinsufficient tumor suppressor. Genes Dev. 2009; 23(23):2700–2704. [PubMed: 19903759]
27. Di Leva G, Gasparini P, Piovan C, Ngankeu A, Garofalo M, Taccioli C, et al. MicroRNA cluster 221-222 and estrogen receptor alpha interactions in breast cancer. J Natl Cancer Inst. 2010; 102(10):706–721. [PubMed: 20388878]
28. Stinson S, Lackner MR, Adai AT, Yu N, Kim HJ, O'Brien C, et al. TRPS1 targeting by miR-221/222 promotes the epithelial-to-mesenchymal transition in breast cancer. Sci Signal. 2011; 4(177):ra41. [PubMed: 21673316]
29. Hwang MS, Yu N, Stinson SY, Yue P, Newman RJ, Allan BB, et al. miR-221/222 targets adiponectin receptor 1 to promote the epithelial-to-mesenchymal transition in breast cancer. PLoS One. 2013; 8(6):e66502. [PubMed: 23776679]
30. Nassirpour R, Mehta PP, Baxi SM, Yin MJ. miR-221 promotes tumorigenesis in human triple negative breast cancer cells. PLoS One. 2013; 8(4):e62170. [PubMed: 23637992]
31. Garofalo M, Di Leva G, Romano G, Nuovo G, Suh SS, Ngankeu A, et al. miR-221&222 regulate TRAIL resistance and enhance tumorigenicity through PTEN and TIMP3 downregulation. Cancer Cell. 2009; 16(6):498–509. [PubMed: 19962668]
32. Su A, He S, Tian B, Hu W, Zhang Z. MicroRNA-221 mediates the effects of PDGF-BB on migration, proliferation, and the epithelial-mesenchymal transition in pancreatic cancer cells. PLoS One. 2013; 8(8):e71309. [PubMed: 23967190]

33. Qin J, Luo M. MicroRNA-221 promotes colorectal cancer cell invasion and metastasis by targeting RECK. FEBS Lett. 2013
34. Pichiorri F, Palmieri D, De Luca L, Consiglio J, You J, Rocci A, et al. In vivo NCL targeting affects breast cancer aggressiveness through miRNA regulation. J Exp Med. 2013; 210(5):951–968. [PubMed: 23610125]
35. Pickering BF, Yu D, Van Dyke MW. Nucleolin protein interacts with microprocessor complex to affect biogenesis of microRNAs 15a and 16. J Biol Chem. 2011; 286(51):44095–44103. [PubMed: 22049078]
36. Martello G, Rosato A, Ferrari F, Manfrin A, Cordenonsi M, Dupont S, et al. A MicroRNA targeting dicer for metastasis control. Cell. 2010; 141(7):1195–1207. [PubMed: 20603000]
37. Li X, Zhang Y, Shi Y, Dong G, Liang J, Han Y, et al. MicroRNA-107, an oncogene microRNA that regulates tumour invasion and metastasis by targeting DICER1 in gastric cancer. J Cell Mol Med. 2011; 15(9):1887–1895. [PubMed: 21029372]
38. Su X, Chakravarti D, Cho MS, Liu L, Gi YJ, Lin YL, et al. TAp63 suppresses metastasis through coordinate regulation of Dicer and miRNAs. Nature. 2010; 467(7318):986–990. [PubMed: 20962848]
39. Boominathan L. The tumor suppressors p53, p63, and p73 are regulators of microRNA processing complex. PLoS One. 2010; 5(5):e10615. [PubMed: 20485546]
40. Grelier G, Voirin N, Ay AS, Cox DG, Chabaud S, Treilleux I, et al. Prognostic value of Dicer expression in human breast cancers and association with the mesenchymal phenotype. Br J Cancer. 2009; 101(4):673–683. [PubMed: 19672267]
41. Ma Z, Swede H, Cassarino D, Fleming E, Fire A, Dadras SS. Up-regulated Dicer expression in patients with cutaneous melanoma. PLoS One. 2011; 6(6):e20494. [PubMed: 21698147]
42. Levy C, Khaled M, Robinson KC, Veguilla RA, Chen PH, Yokoyama S, et al. Lineage-specific transcriptional regulation of DICER by MITF in melanocytes. Cell. 2010; 141(6):994–1005. [PubMed: 20550935]
43. Volinia S, Calin GA, Liu CG, Ambs S, Cimmino A, Petrocca F, et al. A microRNA expression signature of human solid tumors defines cancer gene targets. Proc Natl Acad Sci U S A. 2006; 103(7):2257–2261. [PubMed: 16461460]
44. Sun R, Fu X, Li Y, Xie Y, Mao Y. Global gene expression analysis reveals reduced abundance of putative microRNA targets in human prostate tumours. BMC Genomics. 2009; 10:93. [PubMed: 19245699]
45. Das AK, Carmichael GG. ADAR editing wobbles the microRNA world. ACS Chem Biol. 2007; 2(4):217–220. [PubMed: 17455896]
46. Mobley AK, Braeuer RR, Kamiya T, Shoshan E, Bar-Eli M. Driving transcriptional regulators in melanoma metastasis. Cancer Metastasis Rev. 2012; 31(3–4):621–632. [PubMed: 22684365]
47. Lujambio A, Calin GA, Villanueva A, Ropero S, Sanchez-Cespedes M, Blanco D, et al. A microRNA DNA methylation signature for human cancer metastasis. Proc Natl Acad Sci U S A. 2008; 105(36):13556–13561. [PubMed: 18768788]
48. Meng X, Wu J, Pan C, Wang H, Ying X, Zhou Y, et al. Genetic and Epigenetic Down-regulation of MicroRNA-212 Promotes Colorectal Tumor Metastasis via Dysregulation of MnSOD. Gastroenterology. 2013; 145(2):426–436. e426. [PubMed: 23583431]
49. Haga CL, Phinney DG. MicroRNAs in the imprinted DLK1-DIO3 region repress the epithelial-to-mesenchymal transition by targeting the TWIST1 protein signaling network. J Biol Chem. 2012; 287(51):42695–42707. [PubMed: 23105110]
50. Wang P, Chen L, Zhang J, Chen H, Fan J, Wang K, et al. Methylation-mediated silencing of the miR-124 genes facilitates pancreatic cancer progression and metastasis by targeting Rac1. Oncogene. 2013
51. Lujambio A, Esteller M. CpG island hypermethylation of tumor suppressor microRNAs in human cancer. Cell Cycle. 2007; 6(12):1455–1459. [PubMed: 17581274]
52. Lin CW, Chang YL, Chang YC, Lin JC, Chen CC, Pan SH, et al. MicroRNA-135b promotes lung cancer metastasis by regulating multiple targets in the Hippo pathway and LZTS1. Nat Commun. 2013; 4:1877. [PubMed: 23695671]

53. Zhang L, Yang F, Yuan JH, Yuan SX, Zhou WP, Huo XS, et al. Epigenetic activation of the MiR-200 family contributes to H19-mediated metastasis suppression in hepatocellular carcinoma. Carcinogenesis. 2013; 34(3):577–586. [PubMed: 23222811]
54. Ciafre SA, Galardi S, Mangiola A, Ferracin M, Liu CG, Sabatino G, et al. Extensive modulation of a set of microRNAs in primary glioblastoma. Biochem Biophys Res Commun. 2005; 334(4): 1351–1358. [PubMed: 16039986]
55. Chan JA, Krichevsky AM, Kosik KS. MicroRNA-21 is an antiapoptotic factor in human glioblastoma cells. Cancer Res. 2005; 65(14):6029–6033. [PubMed: 16024602]
56. Meng F, Henson R, Lang M, Wehbe H, Maheshwari S, Mendell JT, et al. Involvement of human micro-RNA in growth and response to chemotherapy in human cholangiocarcinoma cell lines. Gastroenterology. 2006; 130(7):2113–2129. [PubMed: 16762633]
57. Qian B, Katsaros D, Lu L, Preti M, Durando A, Arisio R, et al. High miR-21 expression in breast cancer associated with poor disease-free survival in early stage disease and high TGF-beta1. Breast Cancer Res Treat. 2009; 117(1):131–140. [PubMed: 18932017]
58. Gabriely G, Wurdinger T, Kesari S, Esau CC, Burchard J, Linsley PS, et al. MicroRNA 21 promotes glioma invasion by targeting matrix metalloproteinase regulators. Mol Cell Biol. 2008; 28(17):5369–5380. [PubMed: 18591254]
59. Si ML, Zhu S, Wu H, Lu Z, Wu F, Mo YY. miR-21-mediated tumor growth. Oncogene. 2007; 26(19):2799–2803. [PubMed: 17072344]
60. Xu Y, Sun J, Xu J, Li Q, Guo Y, Zhang Q. miR-21 Is a Promising Novel Biomarker for Lymph Node Metastasis in Patients with Gastric Cancer. Gastroenterol Res Pract. 2012; 2012:640168. [PubMed: 22792096]
61. Zhang BG, Li JF, Yu BQ, Zhu ZG, Liu BY, Yan M. microRNA-21 promotes tumor proliferation and invasion in gastric cancer by targeting PTEN. Oncol Rep. 2012; 27(4):1019–1026. [PubMed: 22267008]
62. Baffa R, Fassan M, Volinia S, O'Hara B, Liu CG, Palazzo JP, et al. MicroRNA expression profiling of human metastatic cancers identifies cancer gene targets. J Pathol. 2009; 219(2):214–221. [PubMed: 19593777]
63. Yan LX, Huang XF, Shao Q, Huang MY, Deng L, Wu QL, et al. MicroRNA miR-21 overexpression in human breast cancer is associated with advanced clinical stage, lymph node metastasis and patient poor prognosis. RNA. 2008; 14(11):2348–2360. [PubMed: 18812439]
64. Song B, Wang C, Liu J, Wang X, Lv L, Wei L, et al. MicroRNA-21 regulates breast cancer invasion partly by targeting tissue inhibitor of metalloproteinase 3 expression. J Exp Clin Cancer Res. 2010; 29:29. [PubMed: 20346171]
65. Lou Y, Yang X, Wang F, Cui Z, Huang Y. 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(6):819–827. [PubMed: 21042775]
66. Chusorn P, Namwat N, Loilome W, Techasen A, Pairojkul C, Khuntikeo N, et al. Overexpression of microRNA-21 regulating PDCD4 during tumorigenesis of liver fluke-associated cholangiocarcinoma contributes to tumor growth and metastasis. Tumour Biol. 2013; 34(3):1579–1588. [PubMed: 23417858]
67. Lee HW, Lee EH, Ha SY, Lee CH, Chang HK, Chang S, et al. Altered expression of microRNA miR-21, miR-155, and let-7a and their roles in pulmonary neuroendocrine tumors. Pathol Int. 2012; 62(9):583–591. [PubMed: 22924844]
68. Zhang JG, Wang JJ, Zhao F, Liu Q, Jiang K, Yang GH. MicroRNA-21 (miR-21) represses tumor suppressor PTEN and promotes growth and invasion in non-small cell lung cancer (NSCLC). Clin Chim Acta. 2010; 411(11-12):846–852. [PubMed: 20223231]
69. Liu ZL, Wang H, Liu J, Wang ZX. MicroRNA-21 (miR-21) expression promotes growth, metastasis, and chemo- or radioresistance in non-small cell lung cancer cells by targeting PTEN. Mol Cell Biochem. 2013; 372(1–2):35–45. [PubMed: 22956424]
70. Shibuya H, Iinuma H, Shimada R, Horiuchi A, Watanabe T. Clinicopathological and prognostic value of microRNA-21 and microRNA-155 in colorectal cancer. Oncology. 2010; 79(3-4):313–320. [PubMed: 21412018]

71. Yang CH, Yue J, Pfeffer SR, Handorf CR, Pfeffer LM. MicroRNA miR-21 regulates the metastatic behavior of B16 melanoma cells. J Biol Chem. 2011; 286(45):39172–39178. [PubMed: 21940630]
72. Han M, Liu M, Wang Y, Chen X, Xu J, Sun Y, et al. Antagonism of miR-21 reverses epithelial-mesenchymal transition and cancer stem cell phenotype through AKT/ERK1/2 inactivation by targeting PTEN. PLoS One. 2012; 7(6):e39520. [PubMed: 22761812]
73. Niu J, Shi Y, Tan G, Yang CH, Fan M, Pfeffer LM, et al. DNA damage induces NF-kappaB-dependent microRNA-21 up-regulation and promotes breast cancer cell invasion. J Biol Chem. 2012; 287(26):21783–21795. [PubMed: 22547075]
74. 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(46):35293–35302. [PubMed: 20826792]
75. Connolly EC, Van Doorslaer K, Rogler LE, Rogler CE. Overexpression of miR-21 promotes an in vitro metastatic phenotype by targeting the tumor suppressor RHOB. Mol Cancer Res. 2010; 8(5): 691–700. [PubMed: 20460403]
76. Asangani IA, Rasheed SA, Nikolova DA, Leupold JH, Colburn NH, Post S, et al. MicroRNA-21 (miR-21) post-transcriptionally downregulates tumor suppressor Pdcd4 and stimulates invasion, intravasation and metastasis in colorectal cancer. Oncogene. 2008; 27(15):2128–2136. [PubMed: 17968323]
77. Zhu S, Wu H, Wu F, Nie D, Sheng S, Mo YY. MicroRNA-21 targets tumor suppressor genes in invasion and metastasis. Cell Res. 2008; 18(3):350–359. [PubMed: 18270520]
78. Huang TH, Wu F, Loeb GB, Hsu R, Heidersbach A, Brincat A, et al. Up-regulation of miR-21 by HER2/neu signaling promotes cell invasion. J Biol Chem. 2009; 284(27):18515–18524. [PubMed: 19419954]
79. Liu LZ, Li C, Chen Q, Jing Y, Carpenter R, Jiang Y, et al. MiR-21 induced angiogenesis through AKT and ERK activation and HIF-1alpha expression. PLoS One. 2011; 6(4):e19139. [PubMed: 21544242]
80. Sheth S, Jajoo S, Kaur T, Mukherjea D, Sheehan K, Rybak LP, et al. Resveratrol reduces prostate cancer growth and metastasis by inhibiting the Akt/MicroRNA-21 pathway. PLoS One. 2012; 7(12):e51655. [PubMed: 23272133]
81. Mudduluru G, George-William JN, Muppala S, Asangani IA, Kumarswamy R, Nelson LD, et al. Curcumin regulates miR-21 expression and inhibits invasion and metastasis in colorectal cancer. Biosci Rep. 2011; 31(3):185–197. [PubMed: 20815812]
82. Weis SM, Cheresh DA. Tumor angiogenesis: molecular pathways and therapeutic targets. Nat Med. 2011; 17(11):1359–1370. [PubMed: 22064426]
83. Viswanathan SR, Daley GQ, Gregory RI. Selective blockade of microRNA processing by Lin28. Science. 2008; 320(5872):97–100. [PubMed: 18292307]
84. King CE, Cuatrecasas M, Castells A, Sepulveda AR, Lee JS, Rustgi AK. LIN28B promotes colon cancer progression and metastasis. Cancer Res. 2011; 71(12):4260–4268. [PubMed: 21512136]
85. Dangi-Garimella S, Yun J, Eves EM, Newman M, Erkeland SJ, Hammond SM, et al. Raf kinase inhibitory protein suppresses a metastasis signalling cascade involving LIN28 and let-7. EMBO J. 2009; 28(4):347–358. [PubMed: 19153603]
86. Yu F, Yao H, Zhu P, Zhang X, Pan Q, Gong C, et al. let-7 regulates self renewal and tumorigenicity of breast cancer cells. Cell. 2007; 131(6):1109–1123. [PubMed: 18083101]
87. Qian P, Zuo Z, Wu Z, Meng X, Li G, Zhang W, et al. Pivotal role of reduced let-7g expression in breast cancer invasion and metastasis. Cancer Res. 2011; 71(20):6463–6474. [PubMed: 21868760]
88. Fu TY, Chang CC, Lin CT, Lai CH, Peng SY, Ko YJ, et al. Let-7b–mediated suppression of basigin expression and metastasis in mouse melanoma cells. Exp Cell Res. 2011; 317(4):445–451. [PubMed: 21087605]
89. Lamouille S, Subramanyam D, Blelloch R, Derynck R. Regulation of epithelial-mesenchymal and mesenchymal-epithelial transitions by microRNAs. Curr Opin Cell Biol. 2013; 25(2):200–207. [PubMed: 23434068]
90. Liang S, He L, Zhao X, Miao Y, Gu Y, Guo C, et al. MicroRNA let-7f inhibits tumor invasion and metastasis by targeting MYH9 in human gastric cancer. PLoS One. 2011; 6(4):e18409. [PubMed: 21533124]

91. Yuva-Aydemir Y, Simkin A, Gascon E, Gao FB. MicroRNA-9: functional evolution of a conserved small regulatory RNA. RNA Biol. 2011; 8(4):557–564. [PubMed: 21697652]
92. Rotkrua P, Akiyama Y, Hashimoto Y, Otsubo T, Yuasa Y. MiR-9 downregulates CDX2 expression in gastric cancer cells. Int J Cancer. 2011; 129(11):2611–2620. [PubMed: 21225631]
93. Guo LM, Pu Y, Han Z, Liu T, Li YX, Liu M, et al. MicroRNA-9 inhibits ovarian cancer cell growth through regulation of NF-kappaB1. FEBS J. 2009; 276(19):5537–5546. [PubMed: 19702828]
94. Ma L, Young J, Prabhala H, Pan E, Mestdagh P, Muth D, et al. miR-9, a MYC/MYCN-activated microRNA, regulates E-cadherin and cancer metastasis. Nat Cell Biol. 2010; 12(3):247–256. [PubMed: 20173740]
95. Zhang H, Qi M, Li S, Qi T, Mei H, Huang K, et al. microRNA-9 targets matrix metalloproteinase 14 to inhibit invasion, metastasis, and angiogenesis of neuroblastoma cells. Mol Cancer Ther. 2012; 11(7):1454–1466. [PubMed: 22564723]
96. Liu N, Sun Q, Chen J, Li J, Zeng Y, Zhai S, et al. MicroRNA-9 suppresses uveal melanoma cell migration and invasion through the NF-kappaB1 pathway. Oncol Rep. 2012; 28(3):961–968. [PubMed: 22825752]
97. Zheng L, Qi T, Yang D, Qi M, Li D, Xiang X, et al. microRNA-9 suppresses the proliferation, invasion and metastasis of gastric cancer cells through targeting cyclin D1 and Ets1. PLoS One. 2013; 8(1):e55719. [PubMed: 23383271]
98. Lu MH, Huang CC, Pan MR, Chen HH, Hung WC. Prospero homeobox 1 promotes epithelial-mesenchymal transition in colon cancer cells by inhibiting E-cadherin via miR-9. Clin Cancer Res. 2012; 18(23):6416–6425. [PubMed: 23045246]
99. Kalluri R. EMT: when epithelial cells decide to become mesenchymal-like cells. J Clin Invest. 2009; 119(6):1417–1419. [PubMed: 19487817]
100. Xia H, Hui KM. MicroRNAs involved in regulating epithelial-mesenchymal transition and cancer stem cells as molecular targets for cancer therapeutics. Cancer Gene Ther. 2012; 19(11):723–730. [PubMed: 22975591]
101. Royer C, Lu X. Epithelial cell polarity: a major gatekeeper against cancer? Cell Death Differ. 2011; 18(9):1470–1477. [PubMed: 21617693]
102. Onder TT, Gupta PB, Mani SA, Yang J, Lander ES, Weinberg RA. Loss of E-cadherin promotes metastasis via multiple downstream transcriptional pathways. Cancer Res. 2008; 68(10):3645–3654. [PubMed: 18483246]
103. Lee JM, Dedhar S, Kalluri R, Thompson EW. The epithelial-mesenchymal transition: new insights in signaling, development, and disease. J Cell Biol. 2006; 172(7):973–981. [PubMed: 16567498]
104. Jing Y, Han Z, Zhang S, Liu Y, Wei L. Epithelial-Mesenchymal Transition in tumor microenvironment. Cell Biosci. 2011; 1:29. [PubMed: 21880137]
105. de Herreros AG, Peiro S, Nassour M, Savagner P. Snail family regulation and epithelial mesenchymal transitions in breast cancer progression. J Mammary Gland Biol Neoplasia. 2010; 15(2):135–147. [PubMed: 20455012]
106. Park SM, Gaur AB, Lengyel E, Peter ME. The miR-200 family determines the epithelial phenotype of cancer cells by targeting the E-cadherin repressors ZEB1 and ZEB2. Genes Dev. 2008; 22(7):894–907. [PubMed: 18381893]
107. Sun L, Yao Y, Liu B, Lin Z, Lin L, Yang M, et al. MiR-200b and miR-15b regulate chemotherapy-induced epithelial-mesenchymal transition in human tongue cancer cells by targeting BMI1. Oncogene. 2012; 31(4):432–445. [PubMed: 21725369]
108. Liu S, Tetzlaff MT, Cui R, Xu X. miR-200c inhibits melanoma progression and drug resistance through down-regulation of BMI-1. Am J Pathol. 2012; 181(5):1823–1835. [PubMed: 22982443]
109. Gregory PA, Bert AG, Paterson EL, Barry SC, Tsykin A, Farshid G, et al. The miR-200 family and miR-205 regulate epithelial to mesenchymal transition by targeting ZEB1 and SIP1. Nat Cell Biol. 2008; 10(5):593–601. [PubMed: 18376396]
110. Bracken CP, Gregory PA, Kolesnikoff N, Bert AG, Wang J, Shannon MF, et al. A double-negative feedback loop between ZEB1-SIP1 and the microRNA-200 family regulates epithelial-mesenchymal transition. Cancer Res. 2008; 68(19):7846–7854. [PubMed: 18829540]

111. Burk U, Schubert J, Wellner U, Schmalhofer O, Vincan E, Spaderna S, 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(6):582–589. [PubMed: 18483486]

112. Korpal M, Lee ES, Hu G, Kang Y. 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(22):14910–14914. [PubMed: 18411277]

113. Kim T, Veronese A, Pichiorri F, Lee TJ, Jeon YJ, Volinia S, et al. p53 regulates epithelial-mesenchymal transition through microRNAs targeting ZEB1 and ZEB2. J Exp Med. 2011; 208(5):875–883. [PubMed: 21518799]

114. Gibbons DL, Lin W, Creighton CJ, Rizvi ZH, Gregory PA, Goodall GJ, et al. Contextual extracellular cues promote tumor cell EMT and metastasis by regulating miR-200 family expression. Genes Dev. 2009; 23(18):2140–2151. [PubMed: 19759262]

115. Roybal JD, Zang Y, Ahn YH, Yang Y, Gibbons DL, Baird BN, et al. miR-200 Inhibits lung adenocarcinoma cell invasion and metastasis by targeting Flt1/VEGFR1. Mol Cancer Res. 2011; 9(1):25–35. [PubMed: 21115742]

116. Hur K, Toiyama Y, Takahashi M, Balaguer F, Nagasaka T, Koike J, et al. MicroRNA-200c modulates epithelial-to-mesenchymal transition (EMT) in human colorectal cancer metastasis. Gut. 2013; 62(9):1315–1326. [PubMed: 22735571]

117. Korpal M, Ell BJ, Buffa FM, Ibrahim T, Blanco MA, Celia-Terrassa T, et al. Direct targeting of Sec23a by miR-200s influences cancer cell secretome and promotes metastatic colonization. Nat Med. 2011; 17(9):1101–1108. [PubMed: 21822286]

118. Kahlert C, Kalluri R. Exosomes in tumor microenvironment influence cancer progression and metastasis. J Mol Med (Berl). 2013; 91(4):431–437. [PubMed: 23519402]

119. Azmi AS, Bao B, Sarkar FH. Exosomes in cancer development, metastasis, and drug resistance: a comprehensive review. Cancer Metastasis Rev. 2013

120. Grange C, Tapparo M, Collino F, Vitillo L, Damasco C, Deregibus MC, et al. Microvesicles released from human renal cancer stem cells stimulate angiogenesis and formation of lung premetastatic niche. Cancer Res. 2011; 71(15):5346–5356. [PubMed: 21670082]

121. Rana S, Malinowska K, Zoller M. Exosomal tumor microRNA modulates premetastatic organ cells. Neoplasia. 2013; 15(3):281–295. [PubMed: 23479506]

122. Roccaro AM, Sacco A, Maiso P, Azab AK, Tai YT, Reagan M, et al. BM mesenchymal stromal cell-derived exosomes facilitate multiple myeloma progression. J Clin Invest. 2013; 123(4): 1542–1555. [PubMed: 23454749]

123. Yang M, Chen J, Su F, Yu B, Lin L, Liu Y, et al. Microvesicles secreted by macrophages shuttle invasion-potentiating microRNAs into breast cancer cells. Mol Cancer. 2011; 10:117. [PubMed: 21939504]

124. Xiao D, Ohlendorf J, Chen Y, Taylor DD, Rai SN, Waigel S, et al. Identifying mRNA, microRNA and protein profiles of melanoma exosomes. PLoS One. 2012; 7(10):e46874. [PubMed: 23056502]

125. Camacho L, Guerrero P, Marchetti D. MicroRNA and Protein Profiling of Brain Metastasis Competent Cell-Derived Exosomes. PLoS One. 2013; 8(9):e73790. [PubMed: 24066071]

126. Tanaka Y, Kamohara H, Kinoshita K, Kurashige J, Ishimoto T, Iwatsuki M, et al. Clinical impact of serum exosomal microRNA-21 as a clinical biomarker in human esophageal squamous cell carcinoma. Cancer. 2013; 119(6):1159–1167. [PubMed: 23224754]

127. Zhuang G, Wu X, Jiang Z, Kasman I, Yao J, Guan Y, et al. Tumour-secreted miR-9 promotes endothelial cell migration and angiogenesis by activating the JAK-STAT pathway. EMBO J. 2012; 31(17):3513–3523. [PubMed: 22773185]

128. Ohshima K, Inoue K, Fujiwara A, Hatakeyama K, Kanto K, Watanabe Y, et al. Let-7 microRNA family is selectively secreted into the extracellular environment via exosomes in a metastatic gastric cancer cell line. PLoS One. 2010; 5(10):e13247. [PubMed: 20949044]

129. Fabbri M, Paone A, Calore F, Galli R, Croce CM. A new role for microRNAs, as ligands of Toll-like receptors. RNA Biol. 2013; 10(2):169–174. [PubMed: 23296026]

130. Broderick JA, Zamore PD. MicroRNA therapeutics. Gene Ther. 2011; 18(12):1104–1110. [PubMed: 21525952]

131. Jackson AL, Levin AA. Developing microRNA therapeutics: approaching the unique complexities. Nucleic Acid Ther. 2012; 22(4):213–225. [PubMed: 22913594]

132. Liu YN, Yin JJ, Abou-Kheir W, Hynes PG, Casey OM, Fang L, et al. MiR-1 and miR-200 inhibit EMT via Slug-dependent and tumorigenesis via Slug-independent mechanisms. Oncogene. 2013; 32(3):296–306. [PubMed: 22370643]

133. Kong X, Li G, Yuan Y, He Y, Wu X, Zhang W, et al. MicroRNA-7 inhibits epithelial-to-mesenchymal transition and metastasis of breast cancer cells via targeting FAK expression. PLoS One. 2012; 7(8):e41523. [PubMed: 22876288]

134. Zhao X, Dou W, He L, Liang S, Tie J, Liu C, et al. MicroRNA-7 functions as an anti-metastatic microRNA in gastric cancer by targeting insulin-like growth factor-1 receptor. Oncogene. 2013; 32(11):1363–1372. [PubMed: 22614005]

135. Wang W, Dai LX, Zhang S, Yang Y, Yan N, Fan P, et al. Regulation of epidermal growth factor receptor signaling by plasmid-based microRNA-7 inhibits human malignant gliomas growth and metastasis in vivo. Neoplasma. 2013; 60(3):274–283. [PubMed: 23373996]

136. Weiss FU, Marques IJ, Woltering JM, Vlecken DH, Aghdassi A, Partecke LI, et al. Retinoic acid receptor antagonists inhibit miR-10a expression and block metastatic behavior of pancreatic cancer. Gastroenterology. 2009; 137(6):2136–2145. e2131-2137. [PubMed: 19747919]

137. Yan Y, Luo YC, Wan HY, Wang J, Zhang PP, Liu M, et al. MicroRNA-10a is involved in the metastatic process by regulating Eph tyrosine kinase receptor A4-mediated epithelial-mesenchymal transition and adhesion in hepatoma cells. Hepatology. 2013; 57(2):667–677. [PubMed: 22996586]

138. Ma L, Reinhardt F, Pan E, Soutschek J, Bhat B, Marcusson EG, et al. Therapeutic silencing of miR-10b inhibits metastasis in a mouse mammary tumor model. Nat Biotechnol. 2010; 28(4): 341–347. [PubMed: 20351690]

139. Takeshita F, Patrawala L, Osaki M, Takahashi RU, Yamamoto Y, Kosaka N, et al. Systemic delivery of synthetic microRNA-16 inhibits the growth of metastatic prostate tumors via downregulation of multiple cell-cycle genes. Mol Ther. 2010; 18(1):181–187. [PubMed: 19738602]

140. Liu S, Goldstein RH, Scepansky EM, Rosenblatt M. Inhibition of rho-associated kinase signaling prevents breast cancer metastasis to human bone. Cancer Res. 2009; 69(22):8742–8751. [PubMed: 19887617]

141. Xu D, Takeshita F, Hino Y, Fukunaga S, Kudo Y, Tamaki A, et al. miR-22 represses cancer progression by inducing cellular senescence. J Cell Biol. 2011; 193(2):409–424. [PubMed: 21502362]

142. Zhang H, Hao Y, Yang J, Zhou Y, Li J, Yin S, et al. Genome-wide functional screening of miR-23b as a pleiotropic modulator suppressing cancer metastasis. Nat Commun. 2011; 2:554. [PubMed: 22109528]

143. Du WW, Fang L, Li M, Yang X, Liang Y, Peng C, et al. MicroRNA miR-24 enhances tumor invasion and metastasis by targeting PTPN9 and PTPRF to promote EGF signaling. J Cell Sci. 2013; 126((Pt 6)):1440–1453. [PubMed: 23418360]

144. Deng M, Tang HL, Lu XH, Liu MY, Lu XM, Gu YX, et al. miR-26a suppresses tumor growth and metastasis by targeting FGF9 in gastric cancer. PLoS One. 2013; 8(8):e72662. [PubMed: 24015269]

145. Yang X, Liang L, Zhang XF, Jia HL, Qin Y, Zhu XC, et al. MicroRNA-26a suppresses tumor growth and metastasis of human hepatocellular carcinoma by targeting interleukin-6-Stat3 pathway. Hepatology. 2013; 58(1):158–170. [PubMed: 23389848]

146. Yu L, Lu J, Zhang B, Liu X, Wang L, Li SY, et al. miR-26a inhibits invasion and metastasis of nasopharyngeal cancer by targeting EZH2. Oncol Lett. 2013; 5(4):1223–1228. [PubMed: 23599767]

147. Gebeshuber CA, Zatloukal K, Martinez J. miR-29a suppresses tristetraprolin, which is a regulator of epithelial polarity and metastasis. EMBO Rep. 2009; 10(4):400–405. [PubMed: 19247375]

148. Fang JH, Zhou HC, Zeng C, Yang J, Liu Y, Huang X, et al. MicroRNA-29b suppresses tumor angiogenesis, invasion, and metastasis by regulating matrix metalloproteinase 2 expression. Hepatology. 2011; 54(5):1729–1740. [PubMed: 21793034]

149. Ru P, Steele R, Newhall P, Phillips NJ, Toth K, Ray RB. miRNA-29b suppresses prostate cancer metastasis by regulating epithelial-mesenchymal transition signaling. Mol Cancer Ther. 2012; 11(5):1166–1173. [PubMed: 22402125]

150. Chou J, Lin JH, Brenot A, Kim JW, Provot S, Werb Z. GATA3 suppresses metastasis and modulates the tumour microenvironment by regulating microRNA-29b expression. Nat Cell Biol. 2013; 15(2):201–213. [PubMed: 23354167]

151. Wang H, Zhu Y, Zhao M, Wu C, Zhang P, Tang L, et al. miRNA-29c suppresses lung cancer cell adhesion to extracellular matrix and metastasis by targeting integrin beta1 and matrix metalloproteinase2 (MMP2). PLoS One. 2013; 8(8):e70192. [PubMed: 23936390]

152. Liu N, Tang LL, Sun Y, Cui RX, Wang HY, Huang BJ, et al. MiR-29c suppresses invasion and metastasis by targeting TIAM1 in nasopharyngeal carcinoma. Cancer Lett. 2013; 329(2):181–188. [PubMed: 23142282]

153. Kumarswamy R, Mudduluru G, Ceppi P, Muppala S, Kozlowski M, Niklinski J, 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(9):2044–2053. [PubMed: 21633953]

154. 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(2–3):209–218. [PubMed: 23486085]

155. Valastyan S, Chang A, Benaich N, Reinhardt F, Weinberg RA. Activation of miR-31 function in already-established metastases elicits metastatic regression. Genes Dev. 2011; 25(6):646–659. [PubMed: 21406558]

156. Guo Y, Li S, Qu J, Wang S, Dang Y, Fan J, et al. MiR-34a inhibits lymphatic metastasis potential of mouse hepatoma cells. Mol Cell Biochem. 2011; 354(1-2):275–282. [PubMed: 21553024]

157. Ahn YH, Gibbons DL, Chakravarti D, Creighton CJ, Rizvi ZH, Adams HP, et al. ZEB1 drives prometastatic actin cytoskeletal remodeling by downregulating miR-34a expression. J Clin Invest. 2012; 122(9):3170–3183. [PubMed: 22850877]

158. Yan K, Gao J, Yang T, Ma Q, Qiu X, Fan Q, et al. MicroRNA-34a inhibits the proliferation and metastasis of osteosarcoma cells both in vitro and in vivo. PLoS One. 2012; 7(3):e33778. [PubMed: 22457788]

159. Yang S, Li Y, Gao J, Zhang T, Li S, Luo A, et al. MicroRNA-34 suppresses breast cancer invasion and metastasis by directly targeting Fra-1. Oncogene. 2013; 32(36):4294–4303. [PubMed: 23001043]

160. Fang L, Du WW, Yang W, Rutnam ZJ, Peng C, Li H, et al. MiR-93 enhances angiogenesis and metastasis by targeting LATS2. Cell Cycle. 2012; 11(23):4352–4365. [PubMed: 23111389]

161. Chen HY, Lin YM, Chung HC, Lang YD, Lin CJ, Huang J, et al. miR-103/107 promote metastasis of colorectal cancer by targeting the metastasis suppressors DAPK and KLF4. Cancer Res. 2012; 72(14):3631–3641. [PubMed: 22593189]

162. Tsai WC, Hsu PW, Lai TC, Chau GY, Lin CW, Chen CM, et al. MicroRNA-122, a tumor suppressor microRNA that regulates intrahepatic metastasis of hepatocellular carcinoma. Hepatology. 2009; 49(5):1571–1582. [PubMed: 19296470]

163. Zheng F, Liao YJ, Cai MY, Liu YH, Liu TH, Chen SP, et al. The putative tumour suppressor microRNA-124 modulates hepatocellular carcinoma cell aggressiveness by repressing ROCK2 and EZH2. Gut. 2012; 61(2):278–289. [PubMed: 21672940]

164. Liang YJ, Wang QY, Zhou CX, Yin QQ, He M, Yu XT, et al. MiR-124 targets Slug to regulate epithelial-mesenchymal transition and metastasis of breast cancer. Carcinogenesis. 2013; 34(3): 713–722. [PubMed: 23250910]

165. Bi Q, Tang S, Xia L, Du R, Fan R, Gao L, et al. Ectopic expression of MiR-125a inhibits the proliferation and metastasis of hepatocellular carcinoma by targeting MMP11 and VEGF. PLoS One. 2012; 7(6):e40169. [PubMed: 22768249]

166. Tang F, Zhang R, He Y, Zou M, Guo L, Xi T. MicroRNA-125b induces metastasis by targeting STARD13 in MCF-7 and MDA-MB-231 breast cancer cells. PLoS One. 2012; 7(5):e35435. [PubMed: 22693547]

167. Feng R, Chen X, Yu Y, Su L, Yu B, Li J, et al. miR-126 functions as a tumour suppressor in human gastric cancer. Cancer Lett. 2010; 298(1):50–63. [PubMed: 20619534]
168. Zhang Y, Yang P, Sun T, Li D, Xu X, Rui Y, 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(3):284–294. [PubMed: 23396050]
169. Liang L, Li X, Zhang X, Lv Z, He G, Zhao W, et al. MicroRNA-137, an HMGA1 target, suppresses colorectal cancer cell invasion and metastasis in mice by directly targeting FMNL2. Gastroenterology. 2013; 144(3):624–635. e624. [PubMed: 23201162]
170. Chen DL, Wang DS, Wu WJ, Zeng ZL, Luo HY, Qiu MZ, et al. Overexpression of paxillin induced by miR-137 suppression promotes tumor progression and metastasis in colorectal cancer. Carcinogenesis. 2013; 34(4):803–811. [PubMed: 23275153]
171. Wong CC, Wong CM, Tung EK, Au SL, Lee JM, Poon RT, et al. The microRNA miR-139 suppresses metastasis and progression of hepatocellular carcinoma by down-regulating Rho-kinase 2. Gastroenterology. 2011; 140(1):322–331. [PubMed: 20951699]
172. Shen K, Liang Q, Xu K, Cui D, Jiang L, Yin P, et al. MiR-139 inhibits invasion and metastasis of colorectal cancer by targeting the type I insulin-like growth factor receptor. Biochem Pharmacol. 2012; 84(3):320–330. [PubMed: 22580051]
173. Luo HN, Wang ZH, Sheng Y, Zhang Q, Yan J, Hou J, et al. miR-139 targets CXCR4 and inhibits the proliferation and metastasis of laryngeal squamous carcinoma cells. Med Oncol. 2014; 31(1): 789. [PubMed: 24318902]
174. Peng X, Guo W, Liu T, Wang X, Tu X, Xiong D, et al. Identification of miRs-143 and −145 that is associated with bone metastasis of prostate cancer and involved in the regulation of EMT. PLoS One. 2011; 6(5):e20341. [PubMed: 21647377]
175. Hu Y, Ou Y, Wu K, Chen Y, Sun W. miR-143 inhibits the metastasis of pancreatic cancer and an associated signaling pathway. Tumour Biol. 2012; 33(6):1863–1870. [PubMed: 23070684]
176. Ma Q, Jiang Q, Pu Q, Zhang X, Yang W, Wang Y, et al. MicroRNA-143 inhibits migration and invasion of human non-small-cell lung cancer and its relative mechanism. Int J Biol Sci. 2013; 9(7):680–692. [PubMed: 23904792]
177. Sachdeva M, Mo YY. MicroRNA-145 suppresses cell invasion and metastasis by directly targeting mucin 1. Cancer Res. 2010; 70(1):378–387. [PubMed: 19996288]
178. Zhang H, Pu J, Qi T, Qi M, Yang C, Li S, et al. MicroRNA-145 inhibits the growth, invasion, metastasis and angiogenesis of neuroblastoma cells through targeting hypoxia-inducible factor 2 alpha. Oncogene. 2012
179. Gao P, Xing AY, Zhou GY, Zhang TG, Zhang JP, Gao C, et al. The molecular mechanism of microRNA-145 to suppress invasion-metastasis cascade in gastric cancer. Oncogene. 2013; 32(4):491–501. [PubMed: 22370644]
180. Zheng L, Pu J, Qi T, Qi M, Li D, Xiang X, et al. miRNA-145 targets v-ets erythroblastosis virus E26 oncogene homolog 1 to suppress the invasion, metastasis, and angiogenesis of gastric cancer cells. Mol Cancer Res. 2013; 11(2):182–193. [PubMed: 23233482]
181. Hurst DR, Edmonds MD, Scott GK, Benz CC, Vaidya KS, Welch DR. Breast cancer metastasis suppressor 1 up-regulates miR-146, which suppresses breast cancer metastasis. Cancer Res. 2009; 69(4):1279–1283. [PubMed: 19190326]
182. Hou Z, Yin H, Chen C, Dai X, Li X, Liu B, et al. microRNA-146a targets the L1 cell adhesion molecule and suppresses the metastatic potential of gastric cancer. Mol Med Rep. 2012; 6(3): 501–506. [PubMed: 22711166]
183. Zhou L, Zhao X, Han Y, Lu Y, Shang Y, Liu C, et al. Regulation of UHRF1 by miR-146a/b modulates gastric cancer invasion and metastasis. FASEB J. 2013; 27(12):4929–4939. [PubMed: 23982143]
184. Zheng B, Liang L, Wang C, Huang S, Cao X, Zha R, et al. MicroRNA-148a suppresses tumor cell invasion and metastasis by downregulating ROCK1 in gastric cancer. Clin Cancer Res. 2011; 17(24):7574–7583. [PubMed: 21994419]
185. Yokobori T, Suzuki S, Tanaka N, Inose T, Sohda M, Sano A, et al. MiR-150 is associated with poor prognosis in esophageal squamous cell carcinoma via targeting the EMT inducer ZEB1. Cancer Sci. 2013; 104(1):48–54. [PubMed: 23013135]

186. Xu Q, Sun Q, Zhang J, Yu J, Chen W, Zhang Z. Downregulation of miR-153 contributes to epithelial-mesenchymal transition and tumor metastasis in human epithelial cancer. Carcinogenesis. 2013; 34(3):539–549. [PubMed: 23188671]

187. Liang Z, Wu H, Reddy S, Zhu A, Wang S, Blevins D, et al. Blockade of invasion and metastasis of breast cancer cells via targeting CXCR4 with an artificial microRNA. Biochem Biophys Res Commun. 2007; 363(3):542–546. [PubMed: 17889832]

188. Xiang X, Zhuang X, Ju S, Zhang S, Jiang H, Mu J, et al. miR-155 promotes macroscopic tumor formation yet inhibits tumor dissemination from mammary fat pads to the lung by preventing EMT. Oncogene. 2011; 30(31):3440–3453. [PubMed: 21460854]

189. Meng Z, Fu X, Chen X, Zeng S, Tian Y, Jove R, et al. miR-194 is a marker of hepatic epithelial cells and suppresses metastasis of liver cancer cells in mice. Hepatology. 2010; 52(6):2148–2157. [PubMed: 20979124]

190. Pencheva N, Tran H, Buss C, Huh D, Drobnjak M, Busam K, et al. Convergent multi-miRNA targeting of ApoE drives LRP1/LRP8-dependent melanoma metastasis and angiogenesis. Cell. 2012; 151(5):1068–1082. [PubMed: 23142051]

191. Yu SJ, Hu JY, Kuang XY, Luo JM, Hou YF, Di GH, et al. MicroRNA-200a promotes anoikis resistance and metastasis by targeting YAP1 in human breast cancer. Clin Cancer Res. 2013; 19(6):1389–1399. [PubMed: 23340296]

192. Peng F, Jiang J, Yu Y, Tian R, Guo X, Li X, et al. Direct targeting of SUZ12/ROCK2 by miR-200b/c inhibits cholangiocarcinoma tumourigenesis and metastasis. Br J Cancer. 2013; 109(12):3092–3104. [PubMed: 24169343]

193. Tucci P, Agostini M, Grespi F, Markert EK, Terrinoni A, Vousden KH, et al. Loss of p63 and its microRNA-205 target results in enhanced cell migration and metastasis in prostate cancer. Proc Natl Acad Sci U S A. 2012; 109(38):15312–15317. [PubMed: 22949650]

194. Penna E, Orso F, Cimino D, Tenaglia E, Lembo A, Quaglino E, et al. microRNA-214 contributes to melanoma tumour progression through suppression of TFAP2C. EMBO J. 2011; 30(10):1990–2007. [PubMed: 21468029]

195. Xu Y, Zhao F, Wang Z, Song Y, Luo Y, Zhang X, et al. MicroRNA-335 acts as a metastasis suppressor in gastric cancer by targeting Bcl-w and specificity protein 1. Oncogene. 2012; 31(11):1398–1407. [PubMed: 21822301]

196. Huang Q, Gumireddy K, Schrier M, le Sage C, Nagel R, Nair S, et al. The microRNAs miR-373 and miR-520c promote tumour invasion and metastasis. Nat Cell Biol. 2008; 10(2):202–210. [PubMed: 18193036]

197. Wang M, Li C, Nie H, Lv X, Qu Y, Yu B, et al. Down-regulated miR-625 suppresses invasion and metastasis of gastric cancer by targeting ILK. FEBS Lett. 2012; 586(16):2382–2388. [PubMed: 22677169]

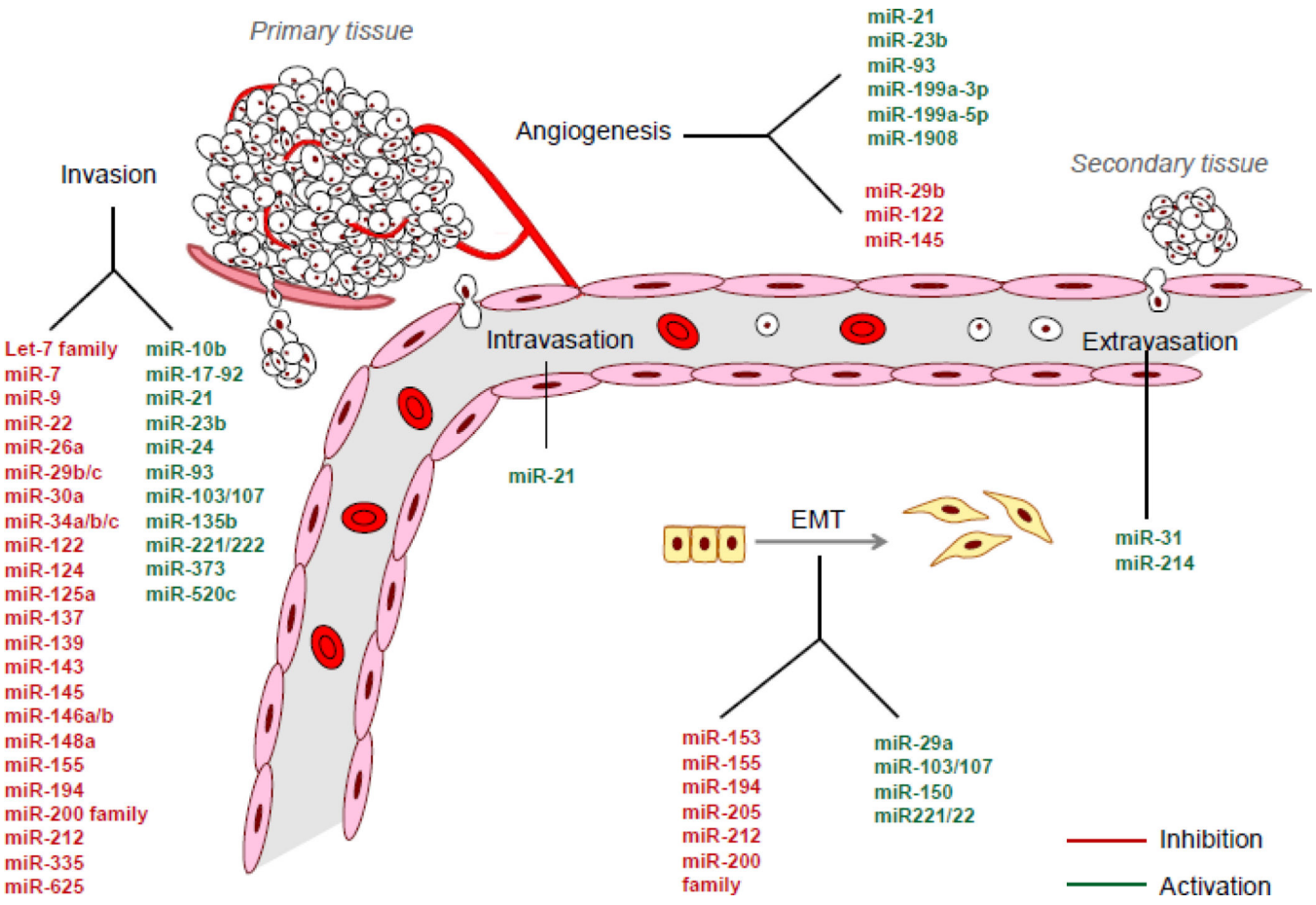

Figure 1.

Table 1

Metastasis-regulating miRNAs

MicroRNA	Properties	Known targets	Type of cancer	References
Let-7 family	Metastasis suppressor Invasion suppressor	HMGA2, H-RAS, MMP11, PBX3, GAB2, FN1, MYH9, Bsg	Breast cancer, Colorectal cancer, Gastric cancer, Melanoma	[86,85,87, 88,90,89]
miR-1	EMT inhibitor	SLUG	Prostate cancer	[132]
miR-7	Metastasis suppressor EMT inhibitor Invasion suppressor	FAK, IGFR, EGFR	Breast cancer, Gastric cancer, Glioma	[133–135]
miR-9	Opposing effects*	CDH1, MMP-14,cyclin D1, Ets1	Breast cancer, Neuroblastoma, Gastric cancer	[94,95,97]
miR-10a	Opposing effects*	EphA4	Liver cancer, Pancreatic cancer	[136,137]
miR-10b	Metastasis promoter Invasion promoter	HOXD10	Breast cancer, Nasopharyngeal carcinoma	[15,138]
miR-15b	EMT inhibitor Metastasis suppressor	BMI1	Tongue squamous cell carcinoma	[107]
miR-16	Metastasis suppressor	CDK, CDK2	Prostate cancer	[139]
miR-17-92	Metastasis promoter Invasion promoter	-	Breast cancer	[140]
miR-21	Metastasis promoter Intravasation promoter Angiogenesis promoter Invasion promoter	PDCD4, maspin, PTEN, BTG2	Colorectal cancer, Prostate cancer, Melanoma, Squamous cell carcinoma	[76,77,81, 71,80,8]
miR-22	Metastasis suppressor Invasion suppressor	CDK6, SIRT1, Sp1	Breast cancer	[141]
miR-23b	Metastasis promoter Angiogenesis promoter Invasion promoter	FZD7, MAP3k1	Colorectal cancer	[142]
miR-24	Metastasis promoter Invasion promoter	PTPN9, PTPRF	Breast cancer	[143]
miR-26a	Metastasis suppressor Invasion suppressor	FGF9, IL-6, EZH2	Gastric cancer, Liver cancer, Nasopharyngeal carcinoma	[144–146]
miR-29a	Metastasis promoter EMT inducer	TTP	-	[147]

MicroRNA	Properties	Known targets	Type of cancer	References
miR-29b	Metastasis suppressor EMT inhibitor Antiangiogenic Invasion suppressor	Snail, ANGPTL4, ITGA6, LOX, VEGF-A, MMP2	Prostate cancer, Breast cancer, Gastric cancer	[148–150]
miR-29c	Metastasis suppressor Invasion suppressor	Integrin β1, MMP2, TIAM1	Lung cancer, Nasopharyngeal carcinoma	[151,152]
miR-30a	Metastasis suppressor EMT inhibitor Invasion suppressor	SNAI1, PIK3CD	Non-small cell lung cancer, Colon cancer	[153,154]
miR-31	Metastasis suppressor Extravasation promoter	RHOA, RDX, ITGA5	Breast cancer	[155]
miR-34a/b/c	Metastasis suppressor Invasion suppressor	Arhgap1, Satb2, lef1, Hnf4a,c-myc, CDK6, CyclinD1, E2F3, Fra-1	Lung cancer, Breast cancer, Liver cancer, Osteosarcoma	[47,156–159]
	Metastasis suppressor			
miR-93	Metastasis promoter Angiogenesis promoter Invasion promoter	LATS2	Breast cancer	[160]
miR-103/107	Metastasis promoter EMT inducer Invasion promoter	DAPK, KLF4, Dicer	Colorectal cancer, Breast cancer	[36,37,161]
miR-122	Metastasis suppressor Antiangiogenic Invasion suppressor	ADAM17	Liver cancer	[162]
miR-124	Metastasis suppressor EMT inhibitor Invasion suppressor	ROCK2, EZH2, Slug	Liver cancer, Breast cancer	[163,164]
miR-125a	Metastasis suppressor Invasion suppressor	VEGF-A, MMP11	Liver cancer	[165]
miR-125b	Metastasis promoter	STARD13	Breast cancer	[166]
miR-126	Metastasis suppressor	SDF-1α, Crk, IGFBP2, MERTK, PITPNC1	Breast cancer, Gastric cancer	[16,167,17,168]
miR-135b	Metastasis promoter Invasion promoter	LATS2, β-TrCP, NDR2, LZTS1	Non-small-cell lung cancer	[52]

MicroRNA	Properties	Known targets	Type of cancer	References
miR-137	Metastasis suppressor Invasion suppressor	FMNL2, PXN	Colorectal cancer	[169,170]
miR-139	Metastasis suppressor Invasion suppressor	IGF-IR	Colorectal cancer, Laryngeal squamous carcinoma, Liver cancer	[171–173]
miR-143	Metastasis suppressor EMT inhibitor Invasion suppressor	CD44v3, GEF1, GEF2, KRAS	Prostate cancer, Non-small cell lung cancer, Pancreatic cancer	[174–176]
miR-145	Metastasis suppressor EMT inhibitor Antiangiogenic Invasion suppressor	HIF-2α, mucin 1, N-cadherin, Ets1	Prostate cancer, Neuroblastoma, Breast cancer, Gastric cancer	[177,174,178–180]
miR-146a/b	Metastasis suppressor Invasion suppressor	LCAM1, UHRF1	Gastric cancer, Breast cancer	[181–183]
miR-148a	Metastasis suppressor Invasion suppressor	TGIF2, ROCK1	Gastric cancer	[47,184]
miR-150	EMT inducer	ZEB1	Esophageal squamous cell carcinoma	[185]
miR-153	Metastasis suppressor EMT inhibitor	SNAI, ZEB2	Epithelial cancer	[186]
miR-155	Opposing effects*	TCF4, CXCR4	Lung cancer, Breast cancer	[187,188]
miR-194	Metastasis suppressor EMT inhibitor Invasion suppressor	N-cadherin	Liver cancer	[189]
miR-199a	Metastasis promoter Angiogenesis promoter	ApoE,DNAJA4	Melanoma	[190]
miR-200 family	Opposing effects*	SLUG, Sec23a, ZEB1, ZEB2, Flt1/VEGFR1, BMI1, YAP1, ROCK2, SUZ12	Prostate cancer, Lung cancer, Tongue squamous cell carcinoma, Melanoma, Breast cancer, Cholangiocarcinoma	[114,115,117,107,108,132,191,192]
miR-205	Metastasis suppressor EMT inhibitor	-	Prostate cancer	[193]
miR-206	Metastasis suppressor	-	Breast cancer	[16]

MicroRNA	Properties	Known targets	Type of cancer	References
miR-212	Metastasis suppressor EMT inhibitor Invasion suppressor	MnSOD	Colorectal cancer	[48]
miR-214	Metastasis promoter Survival to anoikis promoter Extravasation promoter	TFAP2C	Melanoma	[194]
miR-221/222	Metastasis promoter EMT inducer Invasion promoter	TRPS1, ADIPOR1, RECK, PTEN, TIMP3	Colorectal cancer	[31,27,28, 32,29,30,34 ,33]
miR-335	Metastasis suppressor Invasion suppressor	SOX4, TN-C, SP1, Bcl-w	Breast cancer, Gastric cancer	[16,195]
miR-373	Metastasis promoter Invasion promoter	CD44	Breast cancer	[196]
miR-520c	Metastasis promoter Invasion promoter	CD44	Breast cancer	[196]
miR-625	Metastasis suppressor Invasion suppressor	ILK	Gastric cancer	[197]
miR-1908	Metastasis promoter Angiogenesis promoter	ApoE, DNAJA4	Melanoma	[190]

* **miR-9:** a prometastatic and proangiogenic effect was reported in breast cancer[94] while an antimetastatic, invasion suppressive and antiangiogenic effect was demonstrated in neuroblastoma[95] as well as an antimetastatic and invasion suppressive effect in gastric cancer[97].

miR-10a: an antimetastatic effect was demonstrated in pancreatic cancer[136]. In hepatoma, overexpression of miR-10a led to a promotion of migration invasion and EMT of the cells in vitro but its overexpression suppressed metastasis in vivo[137].

miR-155: in breast cancer, ectopic expression of miR-155 in the mammary fat pads of a mouse model prevented tumor dissemination as a result of significantly decreased EMT while injection of this microRNA in the bloodstream significantly promoted macroscopic tumor formation in the lung[188]. In another study, miR-155-mediated inhibition of CXCR4 decreased invasion and metastasis of breast cancer in vitro and in vivo.[187]

miR-200: EMT, invasion and metastasis inhibiting effects have been reported in lung adenocarcinoma[114,115], melanoma[108], tongue squamous cell carcinoma [107] prostate cancer[132] and cholangiocarcinoma[192]. However, a prometastatic effect was demonstrated in breast cancer[117].