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Review

# Regulation of microRNAs in cancer metastasis ☆,☆☆

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## ARTICLE INFO

## 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 to 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.

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## Contents

## 1. 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

a 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′UTRs) 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 (Fig. 1)[13,14]. Among the first metastatic promoter miRNAs to be discovered was miR-10b, identified while screening upregulated miRNAs 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.

## 2. 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 cofactor 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 miRNA 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 cancer [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 miRNAs, such as the miR-221/222 cluster [34] but also miR-21, miR-103 [34] and miR-15a/16 [35]. Furthermore, levels of these miRNAs correlated in breast cancer with NCL. Importantly, NCL targeting led to a decrease of the NCL-dependent miRNAs and an inhibition of breast cancer cell aggressiveness *in vitro* and *in vivo* [34].

The role of the miRNA family miR-103/107 has been recently studied [36]. The 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 was 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 knockout 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].

## 3. 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 miR-34b/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 miR-34b/c and TGIF2 (TGFB-induced factor homeobox 2) for miR-48a, which are oncogenic and metastatic genes. An upregulation of these oncogenes was correlated with miR-34b/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 metastases *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 (NSCLCs), is dually regulated by DNA demethylation and NF-κB 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].

## 4. 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], and 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 antiproliferative 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

**Table 1**
Metastasis-regulating miRNAs.

| MicroRNA | Properties | Known targets | Type of cancer | References |
|---|---|---|---|---|
| Let-7 family | Metastasis suppressor<br>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<br>EMT inhibitor<br>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<br>Invasion promoter | HOXD10 | Breast cancer, nasopharyngeal carcinoma | [15,138] |
| miR-15b | EMT inhibitor<br>Metastasis suppressor | BMI1 | Tongue squamous cell carcinoma | [107] |
| miR-16 | Metastasis suppressor | CDK, CDK2 | Prostate cancer | [139] |
| miR-17-92 | Metastasis promoter<br>Invasion promoter | – | Breast cancer | [140] |
| miR-21 | Metastasis promoter<br>Intravasation promoter<br>Angiogenesis promoter<br>Invasion promoter | PDCD4, maspin, PTEN, BTG2 | Colorectal cancer, prostate cancer, melanoma, squamous cell carcinoma | [76,77,81,71,80,8] |
| miR-22 | Metastasis suppressor<br>Invasion suppressor | CDK6, SIRT1, Sp1 | Breast cancer | [141] |
| miR-23b | Metastasis promoter<br>Angiogenesis promoter<br>Invasion promoter | FZD7, MAP3k1 | Colorectal cancer | [142] |
| miR-24 | Metastasis promoter<br>Invasion promoter | PTPN9, PTPRF | Breast cancer | [143] |
| miR-26a | Metastasis suppressor<br>Invasion suppressor | FGF9, IL-6, EZH2 | Gastric cancer, liver cancer, nasopharyngeal carcinoma | [144–146] |
| miR-29a | Metastasis promoter<br>EMT inducer | TTP | – | [147] |
| miR-29b | Metastasis suppressor<br>EMT inhibitor<br>Antiangiogenic<br>Invasion suppressor | Snail, ANGPTL4, ITGA6, LOX, VEGF-A, MMP2 | Prostate cancer, breast cancer, gastric cancer | [148–150] |
| miR-29c | Metastasis suppressor<br>Invasion suppressor | Integrin β1, MMP2, TIAM1 | Lung cancer, nasopharyngeal carcinoma | [151,152] |
| miR-30a | Metastasis suppressor<br>EMT inhibitor<br>Invasion suppressor | SNAI1, PIK3CD | Non-small cell lung cancer, colon cancer | [153,154] |
| miR-31 | Metastasis suppressor<br>Extravasation promoter | RHOA, RDX, ITGA5 | Breast cancer | [155] |
| miR-34a/b/c | Metastasis suppressor<br>Invasion suppressor | Arhgap1, Satb2, lef1, Hnf4a,c-myc, CDK6, CyclinD1, E2F3, Fra-1 | Lung cancer, breast cancer, liver cancer, osteosarcoma | [47,156–159] |
| miR-93 | Metastasis promoter<br>Angiogenesis promoter<br>Invasion promoter | LATS2 | Breast cancer | [160] |
| miR-103/107 | Metastasis promoter<br>EMT inducer<br>Invasion promoter | DAPK, KLF4, Dicer | Colorectal cancer, breast cancer | [36,37,161] |
| miR-122 | Metastasis suppressor<br>Antiangiogenic<br>Invasion suppressor | ADAM17 | Liver cancer | [162] |
| miR-124 | Metastasis suppressor<br>EMT inhibitor<br>Invasion suppressor | ROCK2, EZH2, Slug | Liver cancer, breast cancer | [163,164] |
| miR-125a | Metastasis suppressor<br>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<br>Invasion promoter | LATS2, β-TrCP, NDR2, LZTS1 | Non-small-cell lung cancer | [52] |
| miR-137 | Metastasis suppressor<br>Invasion suppressor | FMNL2, PXN | Colorectal cancer | [169,170] |
| miR-139 | Metastasis suppressor<br>Invasion suppressor | IGF-IR | Colorectal cancer, laryngeal squamous carcinoma, liver cancer | [171–173] |
| miR-143 | Metastasis suppressor<br>EMT inhibitor<br>Invasion suppressor | CD44v3, GEF1, GEF2, KRAS | Prostate cancer, non-small cell lung cancer, pancreatic cancer | [174–176] |
| miR-145 | Metastasis suppressor<br>EMT inhibitor<br>Antiangiogenic<br>Invasion suppressor | HIF-2α, mucin 1, N-cadherin, Ets1 | Prostate cancer, neuroblastoma, breast cancer, gastric cancer | [177,174,178–180] |

**Table 1** (*continued*)

| MicroRNA | Properties | Known targets | Type of cancer | References |
|---|---|---|---|---|
| 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] |
| 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 a proangiogenic effect was reported in breast cancer [94] while an antimetastatic, an invasion suppressive and an antiangiogenic effect was demonstrated in neuroblastoma [95] as well as an antimetastatic and an 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].

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 miRNAs 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 remodeling 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 suppressive 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 decreased 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 among 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 NF-κB1 [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 to 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 NF-κB 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. This effect is exerted *via* the targeting of the transcription factor Ets1 and of cyclin D1 by miR-9, leading to a dysregulation of their downstream targets, including 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].

## 5. 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 for 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 the 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 miRNAs 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, sensitized 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].

## 6. Exosomal miRNAs and metastasis

Exosomes are 40 to 100 nanometer 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
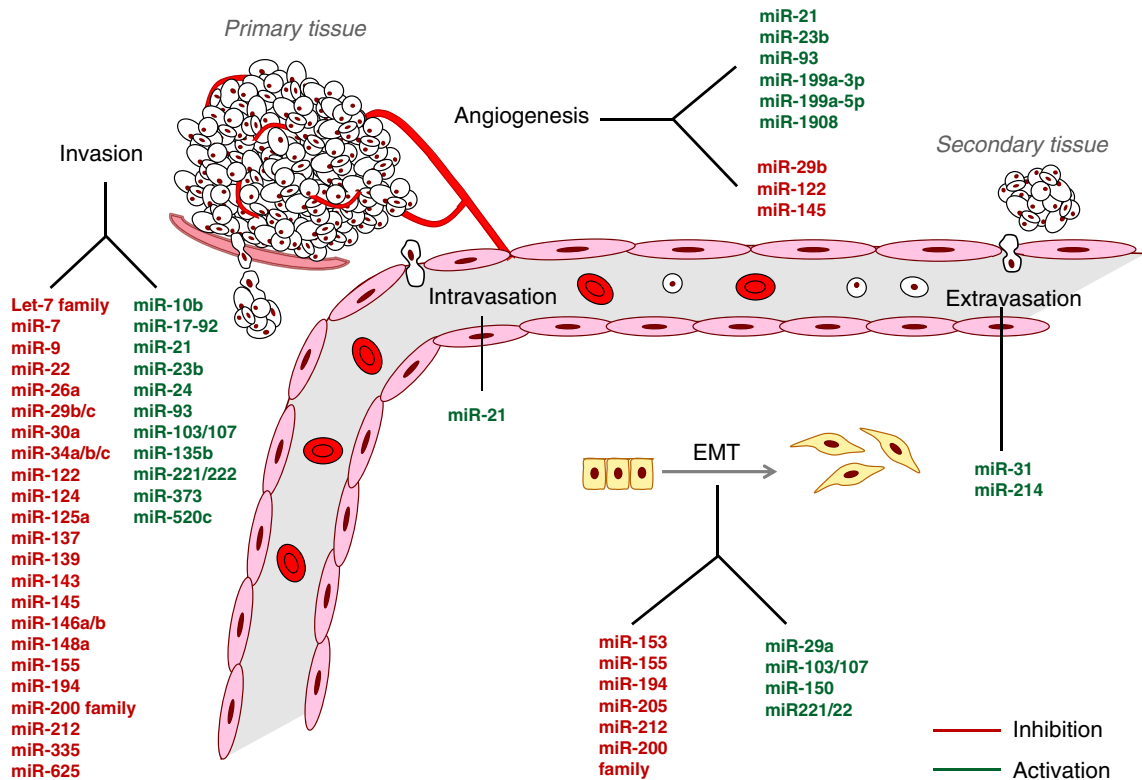
*Primary tissue*

Invasion

Angiogenesis

miR-21
miR-23b
miR-93
miR-199a-3p
miR-199a-5p
miR-1908

miR-29b
miR-122
miR-145

*Secondary tissue*

Let-7 family
miR-7
miR-9
miR-22
miR-26a
miR-29b/c
miR-30a
miR-34a/b/c
miR-122
miR-124
miR-125a
miR-137
miR-139
miR-143
miR-145
miR-146a/b
miR-148a
miR-155
miR-194
miR-200 family
miR-212
miR-335
miR-625

miR-10b
miR-17-92
miR-21
miR-23b
miR-24
miR-93
miR-103/107
miR-135b
miR-221/222
miR-373
miR-520c

Intravasation

miR-21

Extravasation

EMT

miR-31
miR-214

miR-153
miR-155
miR-194
miR-205
miR-212
miR-200
family

miR-29a
miR-103/107
miR-150
miR221/22

Inhibition

Activation

**Fig. 1.** Action of microRNAs on the various steps of cancer metastasis.

macrophages (TAMs) play an important role in promoting tumor cells' invasiveness and ability to form metastases. miR-223, a miRNA specific of TAMs 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 melanocyte 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, activates 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 (TLRs) in surrounding immune cells, thus triggering a prometastatic inflammatory response [129].

## 7. 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 miRNAs and metastasis promoter miRNAs 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.

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