Seminars in Cancer Biology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Seminars in Cancer Biology

journal homepage: www.elsevier.com/locate/semcancer

Review

Role of miRNAs in human cancer metastasis: Implications for therapeutic intervention

Mohammad Alam Jafri [a], Mohammed Hussein Al-Qahtani [a], Jerry William Shay [a,b,*]

[a] Center of Excellence for Genomic Medicine Research, King Abdulaziz University, Jeddah 21589, Saudi Arabia
[b] Department of Cell Biology, University of Texas, Southwestern Medical Center, Dallas, TX 75390, USA

ARTICLE INFO

Article history:
Received 21 December 2016
Received in revised form 3 February 2017
Accepted 6 February 2017
Available online xxx

Keywords:
miRNA
Metastasis
EMT
Anti-OncomiR
MiRNA-mimics

ABSTRACT

Metastasis is the spread and growth of localized cancer to new locations in the body and is considered the main cause of cancer-related deaths. Metastatic cancer cells display distinct genomic and epigenomic profiles and almost universally an aggressive pathophysiology. A better understanding of the molecular mechanisms and regulation of metastasis, including how metastatic tumors grow and survive in the nascent niche and the interactions of the emergent metastatic cancer cells within the local microenvironment may provide tools to design strategies to restrict metastatic dissemination. Aberrant microRNAs (miRNA) expression has been reported in metastatic cancer cells. MicroRNAs are known to regulate divergent and/or convergent metastatic gene pathways including activation of reprogramming switches during metastasis. An in-depth understanding of role of miRNAs in the metastatic cascade may lead to the identification of novel targets for anti-metastatic therapeutics as well as potential candidate miRNAs for cancer treatment. This review primarily focuses on the role of miRNAs in the mechanisms of cancer metastasis as well as implications for metastatic cancer treatment.

Contents

* Corresponding author at: Department of Cell Biology, University of Texas, Southwestern Medical Center, Dallas Texas 75390, USA.
E-mail address: jerry.shay@utsouthwestern.edu (J.W. Shay).

http://dx.doi.org/10.1016/j.semcancer.2017.02.004
1044-579X/

1. Introduction

Cancer remains a leading cause of mortality worldwide. The International Agency for Research on Cancer (IARC) has projected about 22 million new cancer cases and 13 million cancer deaths worldwide by 2030 [1]. In the USA, 1,685,210 new cancer cases and 595,690 cancer-associated deaths have been projected for 2016 [2]. Metastatic cancer is responsible for about 90% of cancer deaths [3] and approximately 50% of all cancer patients present with clinically detectable metastasis at the time of diagnosis, whereas in a large number of patients micrometastases remain undetected by the currently employed techniques [4]. The treatment modalities for metastatic cancer, often based on the information obtained on primary tumors with little or no information on the presence of undetectable metastatic lesions, frequently fail to achieve desired therapy outcomes. Additionally, it is now increasingly being recognized that metastasis is an evolutionary process, where metastatic sub-clones with unique genetic and epigenetic profiles may emerge contributing to a high degree of heterogeneity in therapeutic responses. These factors combined with other limitations of treatment modalities, make management of metastatic cancer extremely difficult [5].

Metastasis involves dissemination of cancerous cells from the primary tumor location to the distant organs via the circulatory system and establishing a secondary tumor at the new tissue site [6]. It is a complex multistep process wherein a subset of dividing cancer cells invades adjacent tissues, enabling cells to penetrate the walls of the surrounding muscle layers, migrate through the extracellular matrix and enter into blood vessels (intravasation) and/or the lymphatic system. The cancer cells then have to survive in the vasculature and engage a mechanism to leave the vasculature (extravasation), thereby spreading (metastasizing) to distant organs. Even once in a distant tissue, the metastatic cell must be able to proliferate in a different extracellular matrix (ECM) niche to produce secondary tumors. While a complex series of individual steps is required, the understanding of the biology of metastasis has recently improved due to availability of advanced imaging and experimental techniques. This has allowed the identification of candidate regulator molecules [7,8], pathways [9] and genes involved in metastasis promotion [10] or its suppression [11]. Investigators have started unraveling underlying mechanisms related to clonal relationships between primary tumor cells and metastatic cells [12,13]. Gene expression profiles that favor interactions between metastatic cells and the local microenvironment have also emerged [14,15] as has organ-specific characteristics of different cancer types and subtypes [16]. However, the exact nature of molecular interactions between diverse factors/molecules within the tissue microenvironment that regulate/modulate movement of cancer cells and their establishment in a nascent niche, is relatively less well understood [17]. Further insights are required for the understanding of those molecular mechanisms that drive the formation of metastasis as well as the precise role of ECM, cell adhesion molecules, epithelial-to-mesenchymal-transition/mesenchymal-to-epithelial-transition (EMT/MET), and signaling dynamics during organ-specific metastasis (such as through cancer cell- secreted extracellular vesicles). Only by a more complete understanding of these molecular mechanisms will we be able to devise new ways to intervene in the metastatic processes.

MicroRNAs have emerged as extremely versatile regulators of cancer-related processes such as cell proliferation, cell cycle arrest, senescence, DNA damage responses and apoptosis. They are single-stranded, small RNA molecules (18–22 nucleotides) with the ability to regulate expression of genes related to almost every biological process. Numerous studies devoted to miRNA expression profiling have shown significantly altered miRNA signatures in various stages of cancer initiation and progression. There is mounting evidence that several miRNAs play a crucial role in regulation of molecular events leading to metastasis and many of these may have potential diagnostic, prognostic and therapeutic values. Therefore, an in-depth understanding of the role of miRNAs in the metastatic processes may provide an opportunity to identify potential novel targets for the development of new interventions or ways to improve current diagnostic and therapeutic approaches to restrict progression of cancer. This review highlights the involvement of miRNAs in various steps of metastasis as well as to identify miRNAs that may have promising therapeutic potential.

1.1. Process of cancer metastasis

Metastasis is a coordinated sequence of events leading to the dissemination of cancer to distant organs through lymphatic and vascular circulatory systems. It is a multistage process (Fig. 1) in which a subset of cancer cells having acquired the ability to escape from the primary site, migrate through the microenvironments, intravasation, capability to survive in the circulation, extravasation, and colonization competence in a new microenvironment can lead to the formation of more aggressive secondary tumors in various parts of the body.

The metastatic cascade starts with the detachment of a small subset of cancer cells from the primary tumor, in part by morphological changes such as epithelial-to-mesenchymal transition (EMT), migration through the ECM, and invasion into the neighboring tissues, intravasation (transendothelial migration into blood vessels), anchorage-independent survival in the circulation, extravasation (exit from the circulation) and colonization and secondary tumor formation [18]. The metastasis cascade is not only dependent on genomic and epigenomic alterations within a subset of cancer cells, but also involves interactions with stromal cells such as cancer-associated fibroblasts (CAFs) and tumor-associated macrophages (TAMs) that may significantly contribute to cancer progression. The lack of extravasating and colonizing cancer cells is a major bottleneck for studies on metastasis. In fact, limited information is available on how migrating cancer cells enter through the endothelium of small capillaries and extravasate through the vascular wall to colonize distant organs. It is not well understood what determines organo-tropic behavior of metastatic cells. The “seed and soil” hypothesis emphasizes availability of a favorable microenvironment for successful metastases formation [19,20] whereas the ‘filter and flow’ concept argues that metastatic colonization occurs at sites of optimal blood flow patterns [21]. A recent report suggests that tumor-derived exosomes (extracellular vesicle) containing pro-EMT signatures induce stromal remodeling and create a favorable “pre-metastatic niche” where incoming metastatic cells may establish metastases [22]. Additionally, whether metastasis is an early or late event in tumor progression remains to be clearly established.

Several models of cancer progression have been proposed including a linear progression model [23] and a parallel progression model [24]. The linear progression model proposes that during early cancer cell proliferation genomic instability increases and some cancer cells undergo successive rounds of changes and selection and accumulate genetic alterations in a step wise manner. This leads to cells acquiring metastatic traits giving rise to specific-clones carrying genomic and epigenomic changes. Thus according to this model metastasis is an end-stage event and the parental tumor cells and metastatic cells share a large number of genomic alterations. Using targeted next generation sequencing on primary colorectal tumors, liver metastasis and normal colonic tissues, 750 genes were analyzed and there was high genomic concordance of primary tumor and metastasis [25] supporting this linear model of cancer progression. Conversely, the parallel progression model argues that tumor cells spread at a very early stage of tumor pro-

Please cite this article in press as: M.A. Jafri, et al., Role of miRNAs in human cancer metastasis: Implications for therapeutic intervention, Semin Cancer Biol (2017), http://dx.doi.org/10.1016/j.semcancer.2017.02.004

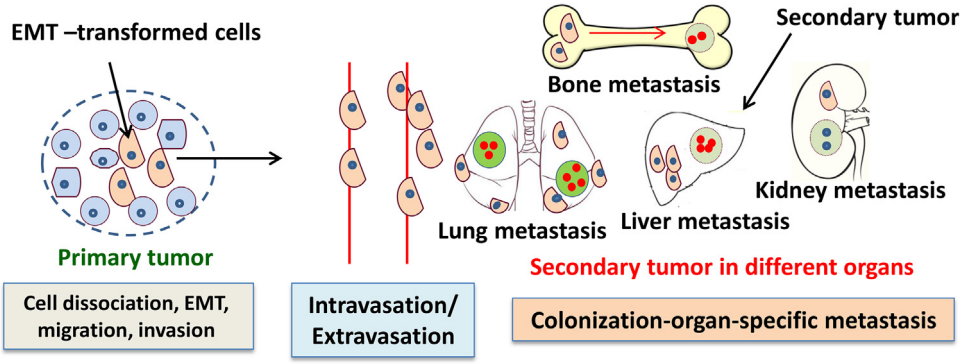

Fig. 1. Metastasis stages: As the primary tumor grows a subset of more epitheliod shaped cells can assume mesenchymal characteristics, migrate through the extracellular matrix, invade blood/lymph vessels, extravasate, and finally colonized distant organs forming more aggressive secondary tumors [18].

gression and acquire a different genetic profile in the metastatic niche depending upon the requirements of the new microenvironment. This model predicts that metastatic cells will have a distinct genomic profile reflective of their separate environments. Several studies using transgenic mouse models for tumor dissemination of various cancer types support this model of metastasis [24]. However, further genomic studies (and epigenomic studies) are needed to help resolve the issues related to clonal evolution of metastatic cells as well as organ-tropism and latency. A more detailed understanding of both these models should significantly contribute to the selection of an appropriate treatment and design for effective preventive measures. Metastasis is also considered to be a very inefficient process because only a fraction of cancer cells with specific characteristics (acquired by specific gene expression changes) successfully complete all metastatic steps and produce secondary tumors. There is a stringent requirement of a highly synchronous interplay of diverse molecular pathways at every step of metastasis and the inability to complete any of these steps will stop the metastatic cascade. It has been reported that about 1×10^6 cancer cells can infiltrate the circulatory system per day but only <0.1% will colonize forming distal metastases [26]. However, an undetectable cancer cell population called micrometastases may remain dormant to produce macrometastases many years following cancer treatment [27].

1.2. miRNAs: biogenesis and mechanism of action

The biogenesis of miRNAs, mechanism of action and their role in living systems have been extensively reviewed [28]. Briefly, biogenesis of miRNAs starts with the transcription of miRNA genes by RNA polymerase II to form 1–3 kb long transcripts called primary-miRNAs (pri-miRNAs) containing a seed sequence (complementary to the target area on mRNA) folded into stem and loop structures (Fig. 2). Pri-miRNAs are acted upon by Drosha (RNA polymerase III enzyme) and DiGeorge syndrome critical region 8 (DGCR8) protein to generate a 60–100 nucleotide long, hairpin-shaped precursor miRNAs (pre-miRNAs). The pre-RNAs are transferred to the cytoplasm by Exportin-5 (RNA-binding protein) and Ran/GTP. In the cytoplasm, pre-miRNAs are cleaved by Dicer (RNase III) into 10–24 nucleotide long double-stranded miRNAs (ds-miRNAs). One of the strands of ds-miRNA matures as miRNA and second strand is usually degraded. The miRNA is loaded onto the RNA-induced silencing complex (RISC). The mature miRNA sequence guides the miRNA-RISC complex to its target mRNA to bind the 3′ UTR (untranslated) region, to form an imperfect duplex and induce translational repression and/or mRNA decay (Fig. 2).

1.3. MicroRNAs regulate cancer cell detachment, epithelial-to-mesenchymal transition, migration and invasion

MicroRNAs play an essential role in the regulation of different stages of multistep metastatic process (Fig. 3). They control expression of pro-metastatic genes in diverse cancer types to promote or repress metastasis through a variety of molecular mechanisms. A clear understanding of the nature and number of miRNAs involved in metastasis may lead to the further insights on how miRNAs regulate multiple mechanisms in metastasis.

1.4. Cell detachment

The first step in metastatic transformation is the successful dissociation of cancer cells from the primary, localized tumor. The detachment of cancer cells from a primary tumor is a complex process which involves not only the accumulation of successive genomic and epigenomics changes but also drastic changes in interactions between tumor cells and various stromal cell components of the tumor microenvironment. The normal epithelium architecture is maintained by the interaction of cytoskeletal regulatory proteins, cell–cell adhesion molecules, cell–matrix adhesion molecules and extracellular matrix (ECM) proteins [29]. The cytoskeleton, characterizing cell motility and polarity, is highly dynamic structure and involves constant rates of actin polymerization and depolymerization which is mediated by the members of Rho superfamily of GTPases [30]. MicroRNAs regulate expression of Rho superfamily members by targeting their respective mRNAs. For example, miR-31 inhibits expression of RhoA in breast cancer (BC) [31] and miR-124 targets Rho-associated protein kinase-1 (ROCK-1) which facilitates reorganization of the actin cytoskeleton [32,33]. The trans-membrane glycoprotein E-cadherin mediates the cell–cell adhesion of epithelial cells through homophilic interactions (an adhesion molecule on the surface of one cell binds to the same molecule on the surface of another cell). E-cadherin can be targeted by miRNAs either directly or through regulation of transcription factors. MiR-200c, miR-10b and miR-9 directly inactivate E-cadherin mRNA [34–36] whereas other members of the miR-200 family, miR-192 and miR-205 regulate E-cadherin levels by modulating expression of the transcription factors zinc finger E-box-binding proteins 1 and 2 (ZEB1/ZEB2) that can repress the E-cadherin gene in cancer cells [37]. In non-small cell lung cancer (NSCLC), miR-574-5c is upregulated and targets protein tyrosine phosphatase receptor type U (PTPRU). The loss of PTPRU results in the inhibition of dephosphorylation of tyrosine residues on β-catenin that induces loss of E-cadherin-mediated cell-adhesion [38]. Cluster of differentiation 44 (CD44) (multifunctional cell

Please cite this article in press as: M.A. Jafri, et al., Role of miRNAs in human cancer metastasis: Implications for therapeutic intervention, Semin Cancer Biol (2017), http://dx.doi.org/10.1016/j.semcancer.2017.02.004

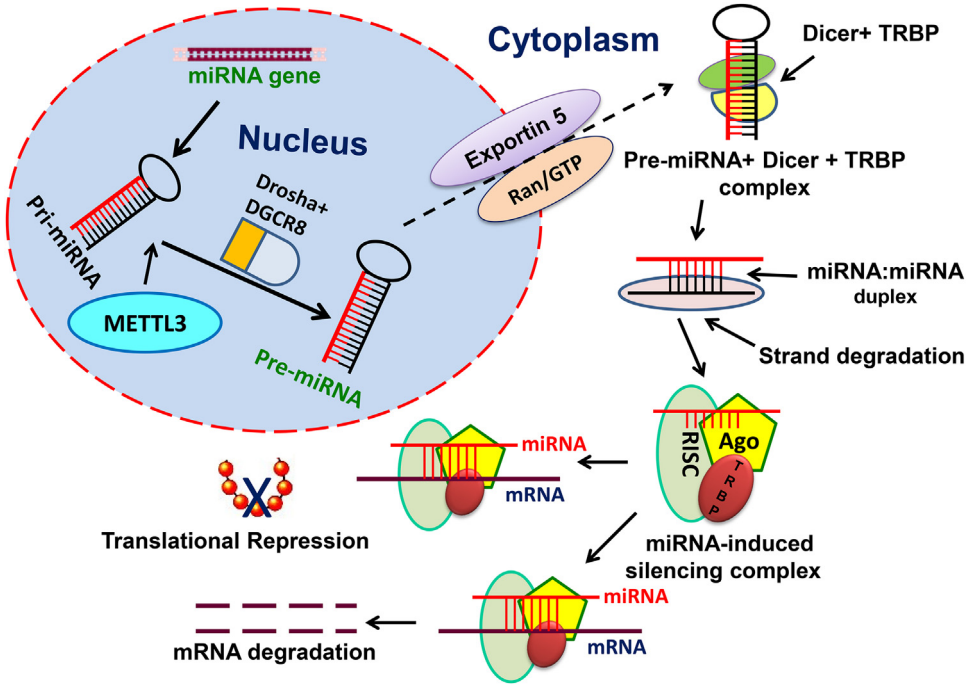

Fig. 2. Biogenesis and mechanism of mRNA repression: RNA polymerase II transcribes miRNA genes as transcripts of 60–100 nucleotide called primary-miRNAs (pri-miRNAs) which are then methylated by methyl trasferase-like3 (METTL3) (anenzymeinvolvedinpost-transcriptional methylation). This permits pri-miRNAs to be recognized by Drosha. Pri-miRNAs are then cleaved by a microprocess or consisting of DGCR8(RNA-bindingprotein) and Drosha (RNasetypeIII) into stem-loop structures called pre-miRNAs. The specific cleavage of pri-miRNAs generates' specific nucleotide sequences', complementary to target area sonmRNA. Pre-miRNAs are then transported to the cytoplasm by a complex of Exportin5/Ran/GTP where they are recruited by TRBP to another RN a setype III enzyme, Dicer, which fragments the minto 20–24 nucleotide long double-stranded miRNAs. One of the strands is degraded and these condstrand becomes a mature miRNA. The mature miRNA is incorporated into a protein complex termed RISC(RISC+Argonaute). The miRISC complex binds with its complimentary target sequence on mRNA to mediate gene silencing via translational repression or degradation of target mRNA [28].

surface molecule) is also involved in cell–cell and cell-matrix interaction through heterophilic interactions (an adhesion molecule functions as a receptor that binds to a different but specific molecule, known as the ligand on the other cell). The CD44 ligands include hyaluronic acid, osteopontin, serglycin, collagens, fibronectin, and laminin. Numerous miRNAs including let-7, miR-30, miR-34, miR-141, miR-143, miR-193, miR-200-a/b/c, miR-320 and miR-451 regulate CD44 expression in cancers [39]. The focal adhesions (contact points between ECM and cytoskeleton) significantly contribute to cellular adhesion with the ECM. Several miRNAs such as miR-7, miR-27 and miR-151 control expression of the focal adhesion kinase (FAK) that mediates focal adhesions [40,41]. The members of the integrin family are key mediators of cell–matrix interactions and several miRNAs have been found to regulate the expression levels of specific integrins. For example, miR-29 and miR-31 directly regulate integrin β1 expression in cancer cells [42,43] and miR-92a reduces *integrin* α5 expression levels in ovarian cancer [44]. ECM proteins collagens, laminins, fibronectin are also involved in cell adhesion and their deregulation facilitates cancer cell dissociation. The expression of these proteins is regulated by miRNAs. MiR-143 regulates expression of collagen type III expression in gastric cancer (GC) [45]. MicroRNA-218 and miR-29 target *laminin*-332 and laminin γ2 (LAMC2) respectively in head and neck squamous cell *carcinoma* [46,47]. Fibronectin expression can be regulated by miR-17 [48]. Matrix remodeling in tumors enhances the dissociation of tumor cells from their native tissue by creating a microenvironment permissive of cancer cell to escape [49]. The cancer-associated fibroblasts and tumor-associated macrophages produce matrix metalloproteinases (MMPs) to remodel the ECM of tumors. Additionally, the extracellular amine oxidases called lysyl oxidases (LOX) particularly lysyl oxidase-like 2 (LOXL2) (overexpressed in cancer cells) promote cell detachment and migration by ECM modulation through crosslinking collagen I fibers [50]. MicroRNAs regulate expression of enzymes involved in modulation of ECM including MMPs and LOX by degrading their respective mRNAs in malignant cells. The downregulation of miR-29c in lung cancer is associated with the inhibition of integrin 1 and MMP2 expression leading to reduced cell adhesion of lung cancer cells to the ECM [51]. Similarly, expression of the lysyl oxidase-like 2 (LOXL2) gene is directly controlled by the members of microRNA-29 family in lung squamous cell carcinoma, head and neck squamous cell carcinoma and renal cell carcinoma [52–54]. Furthermore, miR-211 which is downregulated in most cancers, suppresses expression of secreted protein acidic and rich in cysteine (SPARC) in hepatocellular carcinoma (HCC) [55]. The SPARC is a member of matricellular protein family which is secreted in ECM and regulates cell adhesion [56]. Thus, numerous miRNAs regulate expression of enzymes/factors which are involved in the modulation of ECM and the microenvironment resulting in cell detachment.

1.5. Epithelial-to-mesenchymal transition

The vast majority of cancers trace their origin from epithelial cells. In the early stages, the dividing malignant cells retain epithelial characteristics such as E-cadherin expression, an ability to form a continuous layer of polygonally shaped cells, but lack of motility. Conversely, as tumor mass grow, a subset of cells convert from epithelial to mesenchymal characteristics including increased motility and invasiveness. As the tumor progresses, the loss of cell adhesion stimulates tumor cell dissociation and altered cell-matrix interactions enabling some cells to migrate by abrogating the underlying basement membrane and then invading into adjacent stromal compartments. To spread, epithelial tumor cells

Please cite this article in press as: M.A. Jafri, et al., Role of miRNAs in human cancer metastasis: Implications for therapeutic intervention, Semin Cancer Biol (2017), http://dx.doi.org/10.1016/j.semcancer.2017.02.004

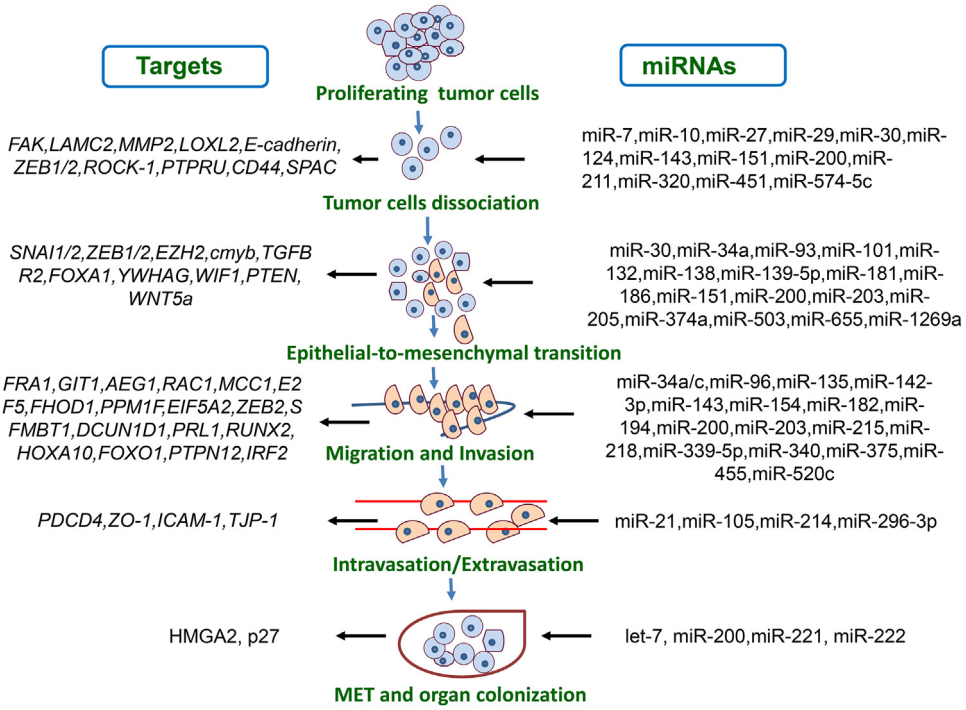

Fig. 3. Schematic representation of miRNAs and their targets at various stages of the metastatic cascade: Rapidly dividing primary tumor cells start dissociating and numerous miRNAs modulate expression of genes involved in cell adhesion and tumor microenvironment maintenance to facilitate dissociation of cancer cells from the primary tumor [31–33]. A sub-clone of epithelial tumor cells undergoes the process of EMT. Expression of the EMT-related molecules is regulated by a number of miRNAs which target crucial genes associated with signaling pathways [64,68,69,72]. MicroRNAs can either repress or stimulate migration and invasion of cancer cells by upregulating or down-regulating gene expression of various molecular components responsible for cell motility and integrity of epithelial architecture [86,87]. During intravastion/extravasation, miRNAs disrupt vascular endothelial barriers by targeting tight junction protein ZO-1 [134]. Additionally, Raf kinase inhibitor protein (RKIP) is also involved in intravasation/extravasation. In breast cancer RKIP inhibits downstream targets of let-7, high-mobility group AT-hook 2 (HMGA2) and BTB And CNC Homology 1 (BACH1) (essential for cancer invasion) to repress intravasation [165]. Mesenchymal-to-epithelial transition (MET) of metastatic cells is crucial for colonization and secondary tumor formation. Several reprogramming transcription factor genes, *Oct3/4*, *Sox2*, *Klf4*, and *Myc* are involved in MET [166]. The expression of these genes is regulated by miR-21, miR- 29a and miR-145. MiR-221 and miR-222 are overexpressed in many cancer types and may promote MET and colonization by inducing cell survival through inhibition of p53 upregulated modulator of apoptosis (PUMA) and downregulating cell cycle inhibitor p27 expression [167] (an inverse correlation exists between miR-221/222 expression and p27 levels).

Table 1
miRNAs involved in the process of epithelial-to-mesenchymal-transition.

miRNA	miRNA level status and role		Target	Refs.
	Expression	Function		
miR-30a	Downregulated	EMT-Inhibitor	*SNAI1*	[73]
miR-34a	Downregulated	EMT-Inhibitor	*SNAI1*	[74,75]
miR-101	Downregulated	EMT-Inhibitor	*ZEB1/ZEB2*	[67]
miR-132	Downregulated	EMT-Inhibitor	*ZEB2*	[70,71]
miR-138	Downregulated	EMT-Inhibitor	*ZEB2,vimentin,EZH2*	[72]
miR-139-5p	Downregulated	EMT-Inhibitor	*ZEB1/ZEB2*	[68]
miR-186	Downregulated	EMT-Inhibitor	*TWIST*	[79]
miR-200	Downregulated	EMT-Inhibitor	*ZEB1/ZEB2*	[64]
miR-203	Downregulated	EMT-Inhibitor	*SNAI2*	[76]
miR-205	Downregulated	EMT-Inhibitor	*ZEB1/ZEB2*	[69]
miR-503	Downregulated	EMT-Inhibitor	*c-myb*	[80]
miR-655	Downregulated	EMT-Inhibitor	*ZEB1, TGFBR2*	[66]
miR-93	Upregulated	EMT-Promoter	*FOXA1*	[82]
miR-181b-3p	Upregulated	EMT-Promoter	*YWHAG*	[77]
miR-374a	Upregulated	EMT-Promoter	*WIF1,PTEN,WNT5A*	[85]
miR-503-3p	Upregulated	EMT-Promoter	*SMAD2*	[83]
miR-1269a	Upregulated	EMT-Promoter	*HOXD10*	[84]

take advantage of two important processes: angiogenesis that provides an escape route for the detached cells to enter the circulatory system and metastasize to distant sites and a reversible molecular reprogramming process called epithelial-to-mesenchymal transition (EMT) in which epithelial cells (non-motile) acquire mesenchymal phenotype (motile) that favors cell migration and invasiveness. EMT is characterized by the loss of E-cadherin and apical–basal cell polarity, accompanied by the gain of mesenchymal characteristics as well as an increased expression of mesenchymal markers, such as vimentin, fibronectin, and N-cadherin [57]. In addition to changes in cell morphology, EMT-undergoing cancer cells exhibit an altered gene expression profile and acquire some of the stem cell like characteristics which help them to bypass cellular senescence induced by increasing genomic instability [58]. Several signaling pathways including wingless integrated (Wnt), protein nuclear factor kappa light-chain-enhancer of activated B-

Please cite this article in press as: M.A. Jafri, et al., Role of miRNAs in human cancer metastasis: Implications for therapeutic intervention, Semin Cancer Biol (2017), http://dx.doi.org/10.1016/j.semcancer.2017.02.004

cells (NF-κB), Notch, Hedgehog and growth factor signaling such as transforming growth factor beta (TGF-β), vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), epidermal growth factor (EGF), fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF), manage to coordinately induce or modulate EMT processes [37]. The loss of expression of E-cadherin in epithelial cells is a major molecular event and these signaling pathways stimulate several transcription factors including ZEB1 and ZEB2, SNAIL and TWIST which mediate repression of E-cadherin [59–63]. It is now widely accepted that aberrantly expressed miRNAs in cancer cells play a critically important role in mesenchymal transformation and regulate EMT by modulating expression of genes involved in EMT. However, the molecular stimuli that activate transcription of miRNAs associated with EMT remain largely less well understood. A large number of EMT-mediating miRNAs have been identified (Table 1) that act through the EMT-regulating transcriptional network or by regulating signaling pathways involved in EMT. The EMT-inducing transcription factors ZEB1/ZEB2 promote EMT mainly through repression of E-cadherin and activation of N-cadherin and vimentin. Several miRNAs are known to regulate ZEB1/ZEB2 expression in malignant cells. MicroRNA-200 family (miR200 a,b,c, miR-141,miR-429) of tumor suppressor miRNAs is involved in the inhibition of EMT and stemness as well as functions to reverse chemo-resistance and to modulate cell proliferation and apoptosis [64]. The decreased expression of miR-200 family members has been reported in a wide variety of cancer types including breast cancer, colorectal cancer (CRC), HCC, NSCLC, pancreatic cancer (PCa), renal cell carcinoma (RCC) and prostate cancer (PC) [57]. The miRNA-200 family regulates expression of transcription factors ZEB1/ZEB2 at the post-transcriptional level by inhibiting their mRNA leading to EMT suppression in cancer cells. Recently, an autocrine TGF-β/ZEB/miR-200 signaling regulatory network has been implicated in EMT regulation in tumor cells. A positive correlation was observed between expression of ZEB1/2 and TGF-β as both stimulate EMT and negative correlations existed between TGF-β and miR-200, as well as between ZEB1/2 and miR-200, in invasive ductal carcinomas [65]. MiR-655 repressed expression of ZEB1 and transforming growth factor beta receptor 2 (TGFBR2) inhibited EMT in several cancer cell lines [66]. In ovarian carcinoma, miR-101 was found to be significantly underexpressed. Overexpression of this miRNA repressed EMT by downregulating the expression of the E-cadherin through directly targeting mRNA of ZEB1/ZEB2 [67]. MiR-139-5p in glioblastoma multiforme (GBM) and miR-205 in CRC suppressed EMT through repression of ZEB1/ZEB2 [68,69]. Mir-132 is downregulated in CRC and NSCLC and its re-expression suppresses ZEB2 expression to inhibit EMT [70,71]. MiR-138 was identified to target mRNAs of ZEB2, vimentin and enhancer of zeste homologue 2 (EZH2) (an epigenetic regulator which modulates the silencing of E-cadherin) to regulate EMT [72].

Numerous miRNAs regulate the expression of transcription factors SNAI1 and SNAI2 (SLUG). MiR-30a expression has been reported to be significantly downregulated in NSCLC tissues [73]. Restoration of miR-30a inhibited EMT by suppressing SNAI1 expression in NSCLC cell lines [74]. The members of miR-34 family (miR-34a, miR-34b and miR-34c) inhibit EMT by downregulating the SNAIl expression [75]. MiR-203/SNAI2/TGFβ form a regulatory loop to control EMT and tumor metastasis in various cancer types [76]. MiR-181b-3p functions as a promoter of Snail-induced EMT in breast cancer by suppressing expression of *YWHAG* gene (also known as tryptophan 5-monooxygenase activation protein gamma). This mediates signal transduction and reduced expression of *YWHAG* induces Snail stabilization leading to activation of EMT [77]. The miRNAs that regulate EMT through transcription factor TWIST include miR-186 in ovarian cancer [78] and prostate cancer [79]. In osteosarcoma, miR-503 expression is downregulated and overexpression of this miRNA inhibits EMT by targeting the transcription factor c-myb [80]. MiR-93 is overexpressed in endometrial carcinoma and promotes EMT by inhibiting expression of the transcription factor FOXA1 (a negative regulator of EMT) [81]. Zhao et al. [82] demonstrated that miR-503-3p was overexpressed in breast cancer cells and promoted EMT by directly targeting smooth muscle actin (SMA) and mothers against decapentaplegic MAD related protein-2 (SMAD2) and E-cadherin. EMT is also promoted by miR-1269a (expression is upregulated) in CRC which forms a positive feedback loop with TGF-β via sex determining region Y)-Box 4 (Sox4), Homeobox D10 (HOXD10) and SMAD7 to promote EMT [83]. A number of miRNAs have been found to suppress/activate the Wnt-signaling pathway by modulating β-catenin to inhibit or promote EMT. MiR-200c was shown to repress Wnt pathway by targeting β-catenin directly in breast cancer [84]. MiR-374a is markedly upregulated in breast cancer and stimulates Wnt/β-catenin signaling cascade to promote EMT by suppressing multiple negative regulators of the Wnt/β-catenin signaling pathway including WNT Inhibitory factor 1(WIF1), phosphatase and tensin homolog (PTEN), and Wnt family member 5A (WNT5A) [85]. In prostate cancer miR-34a inhibits Wnt/β-catenin signaling to repress EMT whereas miR-379 promotes EMT by stimulating it [79]. Taken together, these studies highlight the stringent regulation of EMT progression by miRNAs through modulation of multiple critical genes involved in transcriptional programming, signaling pathways and the maintenance of epithelial architecture.

1.6. Migration and invasion

MiRNAs can promote or inhibit migration and invasion of cancer cells either directly inactivating mRNA or through regulation of expression of downstream effector molecules to control migration and invasion of cancer cells. A large number of miRNAs have been documented to interfere with migration and invasion of tumor cells (Table 2) For example, the miR-200 family inhibits migration and invasion of breast cancer cells by degrading mRNA of multiple proteins including moesin (cytoskeleton-associated protein), ECM protein fibronectin 1, actin-regulatory proteins-formin homology 2 domain containing 1 (FHOD1) and protein phosphatase, Mg^{2+}/Mn^{2+} dependent, 1F (PPM1F) which inhibit migration and invasion through regulation of stress fiber formation [86,87]. MiR-154 is highly underexpressed in breast tumors and overexpression of this miRNA significantly reduces invasiveness of breast cancer cells by targeting mRNA of the E2F transcription factor 5 protein (E2F5) which mediates tumor progression processes [88]. Several miRNAs that target Wnt-signaling can also modulate migration and invasion of breast cancer cells. For example, miR-340 suppressed migration and invasion of breast cancer cells by targeting the Wnt-signaling pathway [89]. MiR-34c is significantly downregulated in breast cancer metastatic tissues and overexpression of this miRNA inhibits a GTPase-activating protein GIT1 expression to suppress migration and invasion of breast cancer cells [90]. MiR-96 and miR-182 levels are upregulated in breast cancer cells [91] and the decreased expression of protein Palladin suppresses breast cancer cell migration and invasion. However, the presence of SNP rs 1071738 at the miR-96/miR-182-binding site within the Palladin 3′-UTR abolished miRNA:mRNA binding, thus diminishing Palladin regulation by these miRNAs. The tumor cells harboring this SNP displayed accelerated migration and invasion. Interestingly, miR-96 can also promote migration and invasion of breast cancer cells by silencing protein tyrosine phosphatase, non-receptor type 9 (PTPN9) mRNA [92]. In HCC, both miR-96 and miR-182 are overexpressed and enhance invasion through downregulation of EphrinA5 expression [93]. The HOX genes such as *HOXA4, HOXA5* and *HOXA10* are deregulated in breast cancer cells and *HOXA10* induces p53 expression to reduce their invasiveness [94]. MiR-135a suppresses

Please cite this article in press as: M.A. Jafri, et al., Role of miRNAs in human cancer metastasis: Implications for therapeutic intervention, Semin Cancer Biol (2017), http://dx.doi.org/10.1016/j.semcancer.2017.02.004

Table 2
miRNAs in migration and invasion (M&I) of cancer cells.

miRNA	miRNA level status and role		Targets	Refs.
	Expression	Function		
miR-34a	Downregulated	Inhibit – M & I	*FRA-1*	[100]
miR-34c	Downregulated	Inhibit – M & I	*GIT1*	[90]
miR-124	Downregulated	Inhibit – M & I	*AEG1*	[107]
miR-142-3p	Downregulated	Inhibit – M & I	*RAC1*	[97]
miR-143	Downregulated	Inhibit – M & I	*MACC1*	[101]
miR-154	Downregulated	Inhibit – M & I	*E2F5*	[88]
miR-154-5p	Downregulated	Inhibit – M & I	*E2F5*	[112]
miR-200	Downregulated	Inhibit – M & I	Moesin,Fibronectin1,*FHOD1*,*PPM1F*	[86,87]
miR-203	Downregulated	Inhibit – M & I	*EIF5A2*	[102]
miR-215	Downregulated	Inhibit – M & I	*ZEB2*	[113]
miR-218	Downregulated	Inhibit – M & I	*SFMBT1*,*DCUN1D1*	[109]
miR-339-5p	Downregulated	Inhibit – M & I	*PRL1*	[104]
miR-340	Downregulated	Inhibit – M & I	Wint-signaling	[89]
miR-375	Downregulated	Inhibit – M & I	*AEG1*	[108]
miR-455	Downregulated	Inhibit – M & I	*RUNX2*	[98]
miR-96	Upregulated	Promote – M & I	Palladin	[91]
miR-135a	Upregulated	Promote – M & I	*HOXA10, FOXO1*	[95,96]
miR-182	Upregulated	Promote – M & I	Palladin	[91]
miR-194	Upregulated	Promote – M & I	*PTPN12*	[111]
miR-520c	Upregulated	Promote – M & I	*IRF2*	[106]

the expression of *HOXA10* to promote cell migration and invasion in breast cancer [95]. It also upregulates the expression of MMP2, SNAIL as well as enhances AKT phosphorylation and decreases forkhead transcriptional factor 1 (FOXO1) phosphorylation. MiR-135a is upregulated in HCC tissues and inhibits FOXO1 expression to stimulate migration and invasion. *FOXO1* is a tumor suppressor and its downregulation accelerates tumor progression in cancer [96]. Invasion and migration of HCC cells is also inhibited by miR-142-3p, downregulated in HCC tissues, via degradation of mRNA of ras-related C3 botulinum toxin substrate 1(RAC1), a GTPase that regulates diverse biological processes including cytoskeletal reorganization, migration and invasion [97]. The expression of miR-455 is strongly downregulated in HCC and inversely correlates with runt-related transcription factor 2 (RUNX2) expression. MiR-455 targets RUNX2 to decrease migration of HCC cells [98]. The RUNX-2 protein is a member of the RUNX family of transcription factors which regulate the transcription of extracellular matrix modulators such as SPARC and MMP1 [99]. MiR-34a, consistently downregulated in CRC, regulates migratory and invasive abilities of CRC cells through a direct action on 3′-UTR of fos-related-antigen-1(FRA-1) mRNA [100]. MiR-143 has been reported to be downregulated in CRC. Overexpression of miR-143 strongly inhibited migration and invasion of CRC cells through repression of metastasis-associated in colon cancer-1(*MACC-1*) gene expression [101]. MiR-203 is frequently downregulated in CRC and its re-expression significantly suppresses cell motility and invasiveness through inactivation of eukaryotic initiation factor 5A2 (*EIF5A2*) gene expression [102]. *EIF5A2* is a major contributor to cell motility and tumor metastasis in diverse cancers [103]. There is significant downregulation of miR-339-5p expression level in CRC tissues [104]. The enhanced expression of miR-339-5p inactivated mRNA of phosphatases of regenerating liver-1 (PRL-1) to suppress CRC cell migration and invasion. The reduced PRL-1 expression is associated with low expression of phosphorylated-extracellular signal-regulated kinase1/2 (p-ERK1/2) which mediates several cancer-related processes including invasion and migration. MiR-146-5p enhances migration and invasion of thyroid carcinoma cells by modulating actin cytoskeleton [105]. In gastric cancer, miR-520c was found to increase migration and invasion by downregulating expression of interferon regulatory factor 2 (IRF2) which is a transcription factor in the interferon gamma signal transduction pathway involved in cancer progression [106]. The expression of miR-124 is downregulated in cervical cancer tissues. Overexpressed miR-124 targeted astrocyte-elevated gene-1 (*AEG1*) to inhibit migration and invasion [107]. *AEG-1* is an oncogene that is overexpressed in all cancers and promotes migration and invasion by activating multiple signal transduction pathways including MEK/ERK, PI3 K/Akt, NF-κB and Wnt/β-catenin. MiR-375 also targets *AEG-1* in HCC to suppress migration and invasion [108]. The overexpression of miR-218, which is significantly underexpressed in cervical cancer, inactivates genes Scm-like with four MBT domains 1 (*SFMBT1)* and defective in cullin neddylation 1, domain containing 1 *(DCUN1D1)* to inhibit cell migration. The elevated expression of *SFMBT1* induces EMT and increases migration and invasiveness of cervical cancer cells, while the overexpression of *DCUN1D1* enhances the migration and invasiveness of cervical cancer cells, but does not induce EMT [109]. The migration and invasion of esophageal tumor cells was increased by miR-20b overexpression which regulated PTEN expression [110]. MiR-194 (overexpressed in ovarian cancer) reduced protein tyrosine phosphatase non-receptor type 12 (PTPN12) expression and promoted migration and invasion. PTPs are signaling molecules that regulate a variety of cellular processes including cytoskeletal structure and cell adhesion by modulating p130 (Cas), CAKbeta/PTK2B, proline-serine-threonine phosphatase interacting protein 1(PSTPIP1), and paxillin [111]. MiR-154-5p, degrades mRNA of the E2F transcription factor 5 (E2F5) to suppress migration and invasion of prostate cancer cells [112]. In NSCLC, miR-215 expression was significantly downregulated which correlated well with lymph node metastasis and advanced TNM stage. Overexpression of miR-215 suppressed ZEB2 expression and inhibited NSCLC cell invasion and migration [113]. In breast cancer cells, miR-34c was downregulated and restored miRNA degraded mRNA of GRK-interacting protein 1 (GIT1) to suppress migration and invasion [90]. The LOXL2 modulates ECM by crosslinking collagen and elastin to promote migration and invasion of cancer cells. Numerous miRNAs have been reported to regulate expression of LOXL2. For example downregulation of miR-26a, miR-26b, miR-29a, miR-29b, miR-29c and miR-218 is associated with the overexpression of LOXL2 in prostate cancer [114].

While regulatory roles of miRNAs have been extensively investigated in carcinomas, their involvement in sarcoma cell migration and invasion is relatively less well studied. The cell invasion in sarcoma cells is often mediated by invadopodia formation, which delivers matrix-degrading enzymes to the invasion interface permitting cancer cell penetration. A novel phosphotyrosine-dependent pathway directs Lyn/Src family tyrosine kinase signals

Please cite this article in press as: M.A. Jafri, et al., Role of miRNAs in human cancer metastasis: Implications for therapeutic intervention, Semin Cancer Biol (2017), http://dx.doi.org/10.1016/j.semcancer.2017.02.004

to the invadopodia to regulate sarcoma cell invasion via the molecule AFAP-1-like-1 (AFAP1L1), a new member of the actin filament-associated protein (AFAP) family [115]. The tumor suppressor miR-138 targets differentiated embryonic chondrocyte gene 2 to inhibit migration and invasion of osteosarcoma cells [116]. In primary mouse sarcomas, miR-182 inhibited sarcoma cell migration and invasion by inactivating genes *RSU1*, *MTSS1*, *PAI1*, and *TIMP1* involved in metastasis. These genes regulate expression of ECM proteases (*PAI1* and *TIMP1),* MMPs *(TIMP1),* focal adhesion complex (*RSU1)* and cytoskeleton remodeling (*MTSS1*) [117]. MiR-16 is extensively downregulated in bone and soft tissue sarcoma. Restoration of miR-16 causes significant reduction of sarcoma cell migration and invasion in a mouse model of soft tissue sarcoma [118]. These studies clearly establish that several miRNAs are coordinated to regulate expression of different genes involved in pathways leading to cancer cell migration and invasion and thus promoting tumor growth and metastasis.

1.7. EMT reprogramming enriches cancer stem cell-like phenotype

EMT is a highly conserved cellular process which is involved in normal embryogenesis and tissue repair. In malignant tumors it enables cells to acquire the ability to migrate to distant sites and to seed secondary tumors. The emerging evidence suggests that rapidly proliferating EMT-undergoing cells acquire cancer stem cell-like properties [119]. EMT is involved in cellular plasticity (a process of identity change) through which cells are believed to obtain hallmark features of stem cells [120]. The cancer stem cells (CSCs) are characterized by their remarkable abilities of self-renewal, maintenance of a quiescent state and multidrug resistance. They have been implicated in tumor recurrence and metastasis [121]. Several studies have reported a link between EMT-undergoing cancer cells and acquisition of molecular signatures of stemness such as expression surface marker CD44 + CD24- as well as genes involved in the maintenance of stem cell phenotype [58,122,123]. In prostate cancer subpopulations of highly invasive cells expressed CD44 + CD24- phenotype and exhibited gene expression profiles consistent with those of prostate CSCs. These invasive cells were highly tumorigenic in NOD/SCID mice compared to the non-invasive cells [124]. Similarly, miR-141 (miR-200 family member) was downregulated in CD^{44+} positive prostate cancer stem cells (PCSCs) obtained from xenografts and patient derived tumors. Ectopic expression of miR-141 in PCSCs inhibited CSC properties via downregulation of pro-metastatic genes including *CD44, Rho GTPase* and *EZH2* [125]. Recently, it has been demonstrated that trypsin-treated low adherent breast and colon cancer cells display a typical profile of EMT-undergoing cell having elevated expression of SLUG, SNAIL, vimentin and N-Cadherin while lacking expression of E-cadherin and claudin [126]. These cells upregulate C-X-C motif chemokine ligand 10 (CXCL10), polycomb group RING finger protein (BMI-1) and octamer-binding transcription factor 4 (OCT4) as well as show differential expression of several miRNAs involved in EMT and/or cell self-renewal such as miR-34a-5p, miR-34c-5p, miR-21-5p, miR-93-5p and miR-100-5p. Additionally, patient-derived xenograft (PDX) models of human breast cancer have revealed that metastatic breast CSCs have a different miRNA expression profiles. For example, miR-33b is downregulated in metastatic breast CSCs and its overexpression significantly inhibits stemness, migration and invasion by targeting high-mobility group AT-hook 2 (*HMGA2*), sal-like protein 4 (*SALL4*) and *TWIST1* [127]. MiR-199a promotes metastatic breast CSC propagation by targeting forkhead box protein P2 (*FOXP2*) gene [128] whereas miR-20a downregulates expression of MHC class I polypeptide-related sequence A (*MICA*) and MHC class I polypeptide-related sequence B (*MICB*). MICA and MICB are two ligands for the stimulatory NK cell receptor NKG2D thus protecting CSCs from the action of NK cells [129]. Furthermore, the miR-200, miR-183, miR-221-222 clusters, as well as let-7, miR-142 and miR-214 directly target genes and pathways (BMI1, Wnt signaling, Notch signaling, and EMT) involved in the maintenance of stemness in breast cancer. Downregulation of these miRNAs enables EMT-undergoing cells to acquire stem cell characteristics [130]. Similarly, several miRNAs including miR-21, miR-34, miR-155, miR-200, miR-221 and miR-1246 are involved in the maintenance of pancreatic cancer stem cells and chemoresistance in pancreatic cancer [131,132]. Thus, miRNAs play a critical role in the phenotypic changes in a subset of undifferentiated cancer cells during EMT that facilitate secondary tumor formation and therapy resistance. Therefore, targeting EMT signaling and CSCs may provide a basis for the development of novel and effective therapeutics for cancer treatment [133]. The replacement or anti-oncomiR therapy with miRNAs involved in the process of EMT and maintenance of cancer stem cells may represent one of the potential options going forward.

1.8. MicroRNAs regulate intravasation and anchorage-independent survival of migrating cancer cells in the circulation

The EMT-transformed migratory cells enter the circulatory or lymphatic systems (intravasation) to reach distant organs. The alteration of tightly controlled vascular endothelial barriers is a critical step for cancer cell intravasation. The endothelial barrier includes an assembly of multiple trans-membrane proteins in the form of intercellular junctions (tight junctions, adherens junctions, and desmosomes) and junctional adhesion molecules to ensure controlled paracellular permeability. While the role of miRNAs in the process of intravasation has not been investigated in detail, emerging evidence suggests that secretory miRNAs of cancer cells mediate expression of genes responsible for maintaining the integrity of endothelium. For example, in breast cancer cells, miR-105 disintegrates the endothelium barrier by degrading mRNA of Zonula Occludens protein-1 (ZO-1) also known as tight junction protein1 (TJP-1) [134]. MiR-21 has also been reported to inhibit intravasation by targeting the programmed cell death 4 (*PDCD4*) tumor suppressor gene in CRC cells [135].The intravasated metastatic cells are denoted as circulating tumor cells (CTCs). CTCs must resist anoikis (cell-detachment-induced apoptosis) and immuno-surveillance in order to survive their journey through circulatory system. The exact molecular nature of strategies adopted by CTCs to withstand the unfavorable environment of blood as well as the function of miRNAs in CTC survival is not clear. However, it has been reported that CTCs acquire stem cell-like phenotype [136], resistance to anoikis and activate receptor tyrosine kinases (RTK) and Wnt-signaling pathways to suppress caspase-related apoptosis to improve survival in the circulation [137]. MiR-296-3p is highly expressed in CTCs of prostate cancer and confers resistance to natural killer cells by targeting intercellular adhesion molecule 1(ICAM-1) also known as CD54 [138]. The increased expression of metastasis-related miRNAs such as miR-21, miR-146a, and miR-210 in CTCs from breast cancer patients has also been reported [139]. However, the functional significance of these miRNAs in CTCs is not clear.

1.9. Role of miRNAs in extravasation and colonization in supportive niches

The process of extravasation starts with the adhesion of CTCs to the endothelium of small capillaries in order to enter into a secondary organ microenvironment. The attachment of CTCs to the endothelium is mediated by endothelial selectins, integrins

Please cite this article in press as: M.A. Jafri, et al., Role of miRNAs in human cancer metastasis: Implications for therapeutic intervention, Semin Cancer Biol (2017), http://dx.doi.org/10.1016/j.semcancer.2017.02.004

and other receptors, including CD-44 and mucins [140]. The final exit of cancer cells from endothelial wall is facilitated by organ-specific chemotactic molecules including cytokines [141]. Little is known with regard to the involvement of miRNAs in the regulation of molecular mechanisms that control extravasation. Some of the miRNAs that have been implicated to play a role in extravasation include miR-105, miR-148b and miR-214. MiR-105 interferes with endothelial wall integrity by disrupting tight junctions through regulation of expression of the TJP-1 gene [134]. Recently, it has been shown that miR-148b and miR-214 can modulate CTC extravasation by controlling expression of cell adhesion molecules integrin alpha 5 (ITGA5) and activate leukocyte cell adhesion molecule (ALCAM) also known as CD166 [142]. CTCs, following extravasation, preferentially colonize distant organs that provide an environment conducive to survival and proliferation. Metastatic colonization is a complex yet inefficient process. A large number of EMT-transformed cells enter the systemic circulation but only a small proportion of cancer cells is able to infiltrate distant organs and successfully establish metastases. Once CTCs reach their new niche, they activate tumor-initiating activity and are denoted as disseminated tumor cells (DTCs). The survival strategy and tumor forming mechanisms of DTCs are a crucial and rate limiting step in metastasis. Although major steps of the colonization process are known, the finer details of the molecular mechanisms involved in secondary tumor formation are poorly understood owing to lack of adequate experimental models to study this complex process. DTC survival may be mediated by interaction between macrophages and vascular cell adhesion molecule-1 (VCAM-1) (also known as CD106) of DTC surface and increased Src kinase activity [143,144]. DTCs can survive tissue microenvironment as dormant cells and miR-23 promotes dormancy in bone metastases of breast cancer cells [145]. DTCs in their supportive niches initiate an EMT reverse program called mesenchymal-to-epithelial transition (MET) that favors colonization [146]. However, details of this mechanism are poorly understood. Similarly, limited information is available on how miRNAs enable colonization. MiRNAs may facilitate creation of 'pre-metastatic niches' which support colonization in different organs by modulating the tissue microenvironment through regulation of stromal cell activity and remodeling of ECM. For example, miR-31, miR-155, miR-214 and miR-511-3p have been shown to interact with various stromal cells to affect tissue microenvironment [147,148].

1.10. Exosomal miRNAs can alter the tissue microenvironment by stromal remodeling to facilitate metastasis

Cell-cell communication between tumor cells and stromal cells is critically important in order to remodel the tissue/tumor microenvironment for pre-metastatic niche formation. The microenvironment of solid tumors mainly consists of two major components i.e. stromal cells and extracellular matrix (ECM). The cellular component of the tumor microenvironment includes cells of hematopoietic origin which are of lymphoid lineage [T-cells, B-cells and natural killer (NK) cells] as well as myeloid lineage (macrophages, neutrophils). The stromal cells of mesenchymal origin mainly include fibroblasts, myofibroblasts, mesenchymal stem cells, adipocytes and endothelial cells. The ECM consists of various proteins, glycoproteins and proteoglycans-structural proteins (collagen and elastin) and specialized proteins (fibrillin. fibronectin and elastin). Thus the tumor cells interact with diverse stromal cell types to modulate the microenvironment supportive to tumor growth, invasion and survival. The tumor exosomes (endosome-derived extracellular vesicles, 30–150 nm in diameter) act as critical messengers receiving and/or conveying signals during communication between tumor and stromal cells. They transfer or transport various biomolecules necessary for tumor microenvironment modulation to create a tumor-supportive niche for subsequent metastatic colonization. The exosomes are associated with the transfer of numerous oncogenic factors to cancer cells as well as to stimulate stromal cells to activate growth promoting mechanisms. For example, the epidermal growth factor receptor variant III (EGFRvIII)-expressing subset of glioma cells, secrets endosomes carrying EGFRvIII in the tissue microenvironment and EGFRvIII-negative cancer cells can uptake it to promote growth by activating mitogen-activated protein kinase (MAPK) and protein kinase B (PKB/Akt) signaling pathways [149]. Interestingly, the tumor stroma-derived exosomes are also believed to modulate functions of tumor cells. Breast cancer-associated fibroblasts secrete exosomes which promote cell motility by activating Wnt-PCP-signaling pathway [150]. Thus exosomes maintain an effective bidirectional communication loop between tumor cells and stromal cells as well as tumor cells and neighboring non-tumor cells to facilitate progression of cancer.

There is mounting evidence, suggesting that miRNAs can be transferred to other cells from the tumor microenvironment to regulate expression of crucial genes involved in migration, invasion, angiogenesis and dormancy. The tumor-derived exosomes play a critical role in the transfer of tumor-associated miRNAs to the deficient tumor cells as well as stromal cells. The tumor-derived exosomes isolated from body fluids (plasma, serum, urine) of cancer patients (ovarian cancer, lung cancer, breast cancer, pancreatic cancer, prostate cancer) show a different miRNA expression pattern compared to non-tumor cells of same type [151]. Numerous exosomal-miRNAs isolated from serum and urine of cancer patients such as miR-17, miR-21, miR-17-92a, miR-141, miR-375, miR-574-3p, miR-1290 have been reported to be associated with metastatic processes including cell adhesion, EMT, migration, invasion and stemness (Fig. 4). MicroRNAs which are frequently detected in exosomes such as miR-21, miR-100-5p, miR-139-5p increase expression of MMP genes and *RANKL* also known as tumor necrosis factor superfamily member 11(*TNFSF-11*) to facilitate migration of prostate cancer cells and may have an important role in the pre-metastatic niche creation [152]. The mesenchymal cells derived from bone marrow secrete miR-23b harboring exosomes which promote dormancy in metastatic breast cancer cells through repression of myristoylated alanine rich protein kinase C substrate (*MARCKS*) gene which regulates cell motility [145,153]. Exosomal miRNAs have also been implicated in the protection of metastatic cells from the immune system. For example, exosomal miR-9 which is overexpressed in many cancer types silences the MHC class I gene thus facilitating escape of tumor cells from the action of immune system [154]. The oncogenic miRNA cluster, miR-17-92, targets cell cycle inhibitors, CDKN1A and CDKN1C, to promote cell proliferation [155]. MiRNAs such as miR-21 and miR-200 stimulate tumor-associated pathways to promote cancer-related processes including angiogenesis, invasion and MET [156]. MiR-223 which is secreted by macrophages promotes invasiveness of recipient cancer cells [157]. The tumor cell-secreted miR-105 disrupts endothelial tight junctions to facilitate migration and invasion of tumor cells [158]. Thus, exosomal-miRNAs can modulate the microenvironment to create a pre-metastatic niche supportive for the colonization of CTCs and secondary tumor formation. However, further studies are required to ascertain the exact role of exosomal-miRNAs in cancer metastasis. Nevertheless, these miRNAs may have potential diagnostic and/or prognostic value.

1.11. MicroRNAs for anti-metastasis therapy in cancer

Metastatic cancer is a difficult to manage condition primarily because of the disseminated nature of the disease and frequent chemoresistance mechanisms to treatment regimens as well as response variability to anticancer drugs. MicroRNAs are emerging

Please cite this article in press as: M.A. Jafri, et al., Role of miRNAs in human cancer metastasis: Implications for therapeutic intervention, Semin Cancer Biol (2017), http://dx.doi.org/10.1016/j.semcancer.2017.02.004

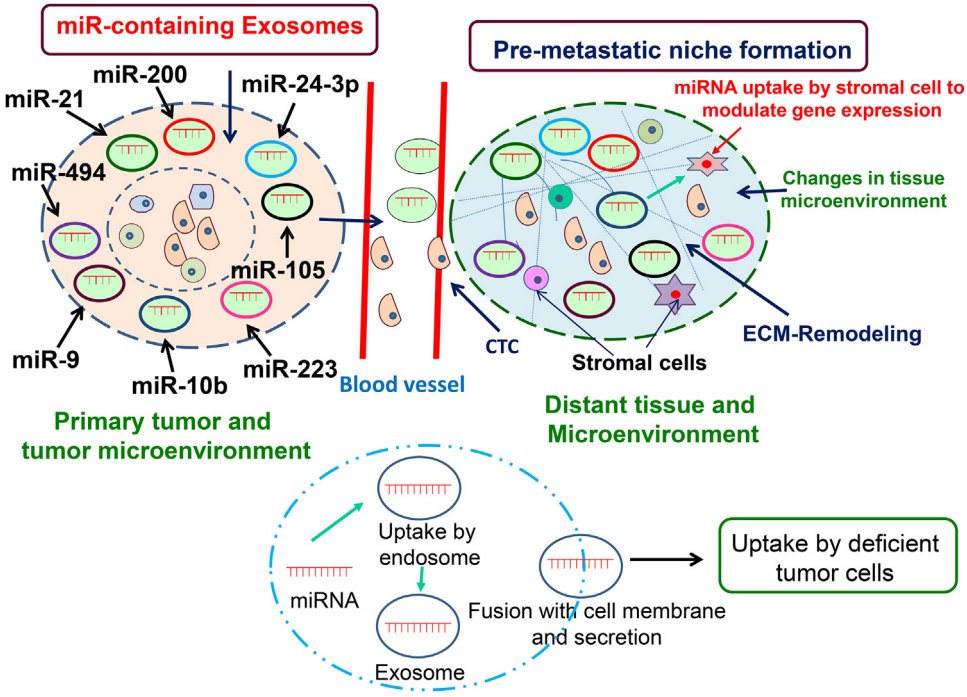

Fig. 4. Tissue microenvironment modulation by tumor-derived exosomal miRNAs: Exosomes are endosome-derived, tumor secreted or non-malignant cell-secreted microvesicles containing diverse bioactive molecules including miRNAs to modulate the tissue microenvironment and various cancer promoting pathways [151]. Exosomal-miRNAs can modulate the local as well as distant tissue microenvironment. They reach distant organ tissues through the circulation and can be taken up by other tumor cells. They can alter the tissue microenvironment by regulating expression of genes involved in various cancer-promoting processes. This may create a pre-metastatic niche favoring metastatic colonization. It is not clear whether endosomal-miRNAs present in the pre-metastatic niche formation are secreted by primary tumor cells only or by CTCs following extravasation. It may be that tumor cells in distant tissues secrete endosomal-miRNAs which can be transferred to recipient stromal cells to modulate their function and make the niche more permissive for tumor growth in a new microenvironment [152,153]. Exosomal miR-9 which is secreted by tumor cells and taken up by deficient tumor cells targets MHC I gene [158], miR-21 promotes tumor-associated pathways and cancer processes including angiogenesis and invasion [168,169], miR-210 also promotes angiogenesis, miR-105 is secreted by metastatic tumor cells and taken up by endothelial cells to increase vascular permeability by downregulating ZO-1 [170], miR-223 is secreted by macrophages and received by tumor cells to promote invasion and tumor cell- secreted miR-10b also promotes invasion [171,172]. miR-200 is secreted by tumor cells and non-malignant cells of the microenvironment receive it to promote MET [173], exosomal miR-24-3p inhibits T-cell function [174], exosomal miR-494 promotes angiogenesis [175].

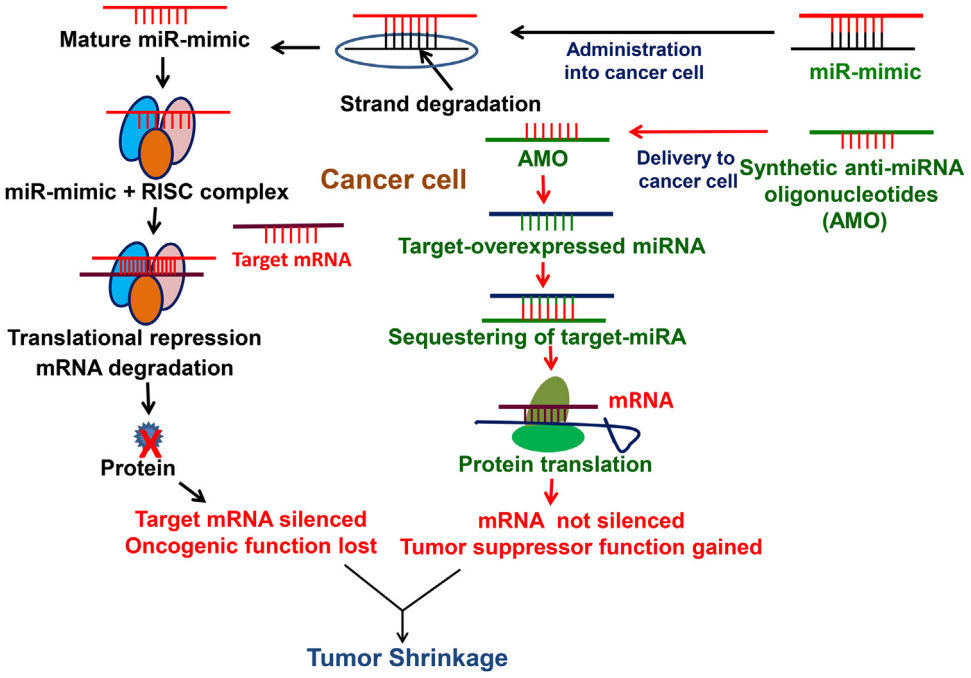

Fig. 5. Schematic representation of miRNA–based therapeutic approaches: At least two approaches can be implemented to treat cancer with miRNA-based therapy. Anti-miRNA oligonucleotides (AMOs) can be delivered to cancer cell to silence function of overexpressed miRNA. AMO inhibits target miRNA so that translation of tumor suppressor mRNA is resumed. The second approach is to use miRNA-mimics to restore function of a downregulated miRNA [176].

Please cite this article in press as: M.A. Jafri, et al., Role of miRNAs in human cancer metastasis: Implications for therapeutic intervention, Semin Cancer Biol (2017), http://dx.doi.org/10.1016/j.semcancer.2017.02.004

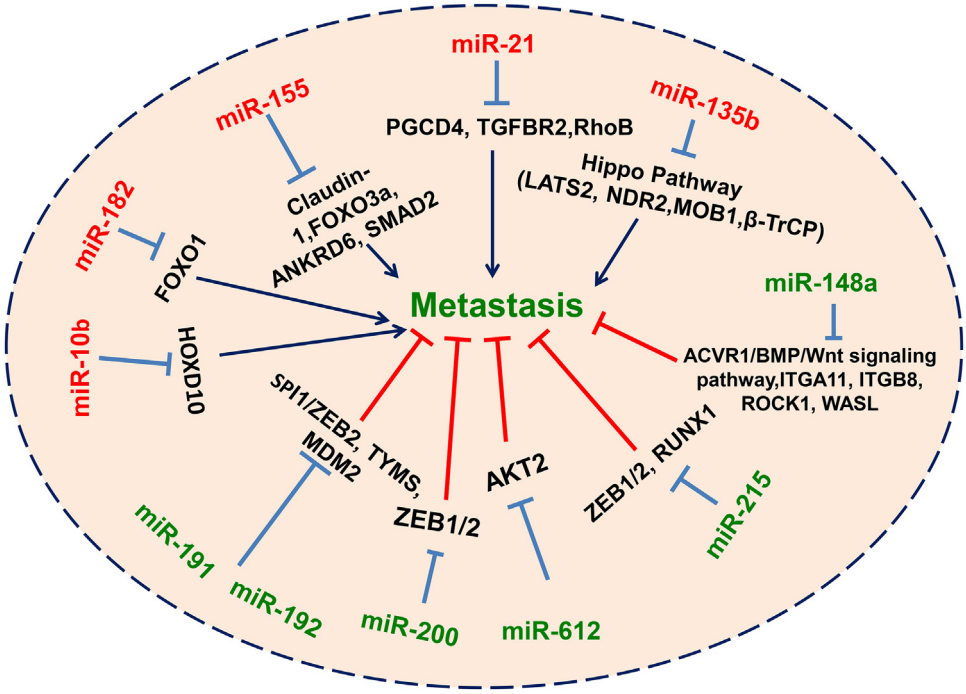

Fig. 6. Potential therapeutic miRNAs: MiR-21, when significantly overexpressed, promotes metastasis by targeting *PGCD4*, *TGFBR2*, and *RhoB* involved in migration and invasion [177]. Upregulated miR-135b promotes metastasis by targeting *MTSS-1* (metastasis suppressor-1), and *LZTS1* (leucine zipper tumor suppressor 1) which is involved in cell-cycle control by interacting with the Cdk1/cyclinB1 complex, multiple components of the Hippo-pathway (Hippo signaling promotes metastasis). It also maintains stemness [178]. MiR-155, when overexpressed targets multiple genes involved in tumor suppression-*FOXO3a* (FOXO acts as a tumor suppressor in a variety of cancers [179]), and cell adhesion-*ANKRD6*, *SMAD2* [180]. Overexpressed miR-182 targets *FOXO1* [181]. Mir-10b, when overexpressed downregulates HOXD10 expression leading to increased expression of *RhoC*, a well characterized prometastatic gene [182]. MiR-148a is downregulated in cancer cells and may be exogenously transferred to cancer cells to suppress metastasis by targeting multiple pathways and genes [183]. Expression of miR-612 is often downregulated and its overexpression leads to the inhibition of AKT2, serine–threonine kinase, involved in several metastasis promoting pathways [184,185]. MiR-200 family members repress *ZEB1/2* expression to inhibit metastasis [65]. MiR-191 and miR-192 are downregulated in cancer cells. Their overexpression leads to inhibition of mRNAs of several transcription factors and proteins which are overexpressed and promote pro-metastasis processes. MiR-191 and miR-192 target important genes such as murine double minute 2 (*MDM2*) which is a negative regulator of *p53*, Smad interacting protein 1 (SPI1) interacts with ZEB2 to promote metastasis, thymidylate synthase (TYMS) is essential for DNA synthesis and repair [186]. MiR-215 represses *ZEB1/2* and *RUNX1* [113,187]. Red color miRNAs are oncomiRs and may be targeted by AMOs to suppress their function. MicroRNAs shown in green color are tumor suppressors and may be used as miRNA-mimics to restore their lost function.

as promising therapeutic candidates and a miR-34-based therapeutic mimic is currently undergoing clinical trials for cancer treatment [159]. Thus, technologies for chemical synthesis, metabolic stability, pharmacokinetic optimization and toxicity manipulation are becoming available. These advances and availability of newly developed *in vivo* models for preclinical evaluation make this field even more attractive. Generally, two approaches are used for miRNA-based therapy. Anti-oncomiR therapy is used to silence the function of overexpressed oncogenic miRNA and miRNA-mimics are used to restore the lost function of downregulated miRNAs (Fig. 5). The activity of oncomiRs can be abrogated to salvage target mRNAs by administration of synthetic anti-miRNA oligonucleotides (AMOs), locked nucleic acid (LNA)-anti-miRNAs and miRNA sponges. These anti-miRs, sequester or degrade mature miRNAs or compete with target mRNA for miRNA binding. In the past few years considerable efforts have been made to identify suitable miRNA candidates, regulating key molecular mechanisms of the metastatic cascade, which may be used as miRNA-based therapy for metastatic cancer. Numerous potential miRNAs have been identified. For example, miR-96 and miR-182 are overexpressed in most cancers and promote migration and invasion of malignant cells and thus may be targeted to inhibit metastasis [91]. Similarly, several other overexpressed miRNAs such as miR-21, miR-181-3p, miR-503-3p, miR-135a/b, miR-155 and miR-520c are also attractive targets for anti-oncomiR silencing. MiRNA-200 family members and other downregulated miRNAs including miR-655, miR-101, miR-205 and miR-132 are potential candidates for replacement therapy in metastasis. However, the most promising therapeutic miRNA candidates include miR- 21, miR-135b, miR-155, miR-182, miR-10b, miR-148a, miR-215, miR-612, miR-200, miR-191 and miR-192 which may be considered for their potential use in anti-metastasis therapy (Fig. 6). Anti-OncomiRs and miRNA-mimics can be targeted to tumors using delivery vehicles such as neutral lipid emulsion [160], polymer nanoparticles [161], solid lipid nanoparticles [162] and liposomes [163]. However, serum stability, tissue penetration and non-specific tissue distribution are limiting factors in effective delivery of miRNAs to the target site. Recently developed vehicles such as a bacterially derived delivery system called the EnGeneIC delivery vehicle (EDV) nano-cells provide stability against serum nucleases as well as the acidic microenvironment of tissues [164]. The nanoparticle-based delivery vehicle has been used for phase I clinical trials studies of MRX-34 (miR-34 mimic) [159]. The therapeutic potential of miRNAs for cancer treatment is well established. However, successful translation of miRNAs into safe and effective cancer therapeutics requires additional and extensive preclinical evaluations of each promising miRNA candidate.

2. Conclusions and future perspective

Metastasis is an enormously complex process. Further studies are needed to gain insights into molecular mechanisms that govern intravasation/extravastion, organ-tropism, latency and colonization. These mechanisms may provide critical information for identification of potential intervention targets for prevention

Please cite this article in press as: M.A. Jafri, et al., Role of miRNAs in human cancer metastasis: Implications for therapeutic intervention, Semin Cancer Biol (2017), http://dx.doi.org/10.1016/j.semcancer.2017.02.004

and/or treatment of metastasis. Currently key unanswered questions include the following:

2.1. The crucial details of miRNA involvement in late stages of metastasis remain to be elucidated

While there is a significant amount of information available on the role of miRNAs in tumor cell dissociation, migration and invasion, how miRNAs regulate distant organ invasion and secondary tumor initiation is much less well understood.

2.2. Treatment of metastatic cancer remain a challenging task

Management of metastatic cancer is difficult and despite the availability of several recently FDA approved anti-metastatic drugs, desired clinical outcomes have not been achieved. Major challenges in the treatment of metastatic cancer are limitations to current imaging and other detection techniques to identify micrometastases, difficulty in eradication of tumor-initiating cancer stem cell-like cells, and rapid emergence of resistance to chemotherapy. Additionally, metastatic cancer cells rapidly evolve towards variant subclones with unique genetic signatures that significantly contribute to tumor heterogeneity and treatment responses. There is thus an urgent medical need to address current clinical limitations in the treatment of metastatic cancer.

2.3. Are microRNAs promising intervention targets and therapeutic candidates?

MicroRNA-based therapy is a relatively new but rational approaches are emerging to repress the action of overexpressed miRNAs as well as to restore lost function of downregulated miRNAs in cancer cells to inhibit tumor growth. Thus, both oncogenic miRNAs (onco-miRs) and tumor suppressive miRNAs are promising candidates for cancer therapy. There are many potential miRNA candidates for miRNA-based therapy for the treatment of metastatic cancer but most of them have not been thoroughly evaluated in currently available patient-derived xenografts and genetically engineered mouse models of metastasis to establish a sound proof-of concept. Therefore, additional and rigorous preclinical studies are required to evaluate their potential as miRNA-based treatments.

Competing interests

The authors declare that there are no conflicts of interest.

Acknowledgements

This work was supported in part by the National Aeronautics and Space Administration NNX16AE08G and NNX15A121G; the National Cancer Institute (Lung SPORE P50CA70907); and the distinguished Southland Financial Corporation Chair in Geriatrics Research to JWS.

References

[1] Global Cancer: Facts and figures: 3rd Edition. Document 044738.pdfwww.cancer.org/acs/groups.
[2] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, CA. Cancer J. Clin. (2016) 7–30.
[3] J. Monteiro, R. Fodde, Cancer stemness and metastasis: therapeutic consequences and perspectives, Eur. J. Cancer 46 (2010) 1198–1203.
[4] M. Winter, R. Gibson, A. Ruszkiewick, S.K. Thomson, Beyond environmental pathology: towards preoperative and intraoperative lymph node staging, Cancer 136 (2015) 743–775.
[5] S. Chakraborty, T. Rahman, The Difficulties in Cancer Treatment, 6 ed., 2012, pp. 16.
[6] S.H. Chan, L.H. Wang, Regulation of cancer metastasis by microRNAs, J. Biomed. Sci. 22 (2015) 9.
[7] P. Raychaudhuri, H.J. Park, FoxM1: a master regulator of tumor metastasis, Cancer Res. 71 (13) (2011) 4229–4233.
[8] T. Yanagishita, I. Yajima, M. Kumasaka, Y. Kawamoto, T. Tsuzuki, Y. Matsumoto, et al., Actin-binding protein, espin: a novel metastatic regulator for melanoma, Mol. Cancer Res. 12 (3) (2014) 440–446.
[9] L. Stone, Bladder cancer: Rho-sensitive pathway mediates metastasis, Nat. Rev. Urol. 13 (2016) 630.
[10] K. Gummireddy, F. Sun, A.J. Klein-Szanta, J.M. Gibbins, P.A. Gimotty, A.J. Saunders, et al., In vivo selection for metastasis promoting genes in the mouse, Proc. Natl. Acad. Sci. U. S. A. 104 (2007) 6696–6701.
[11] D.R. Hurst, D.R. Welch, Metastasis suppressor genes: at the interface between the environment and tumor cell growth, Int. Rev. Cell Mol. Biol. 286 (2011) 107–180.
[12] C.L. Chaffer, R.A. Weinberg, A perspective on cancer cell metastasis, Science 331 (2011) 1559–1564.
[13] L. Ding, M.J. Ellis, S. Li, D.E. Larson, K. Chen, J.W. Wallis, et al., Genome remodelling in a basal-like breast cancer metastasis and xenograft, Nature 464 (2010) 999–1005.
[14] J.A. Joyce, J.W. Pollard, Microenvironmental regulation of metastasis, Nat. Rev. Cancer 9 (2009) 239–252.
[15] Y. Zhang, P. Yang, X.F. Wang, Microenvironmental regulation of cancer metastasis by miRNAs, Trends Cell Biol. 24 (3) (2014) 153–160.
[16] P.D. Ottewell, L. O'Donnell, I. Holen, Molecular alterations that drive breast cancer metastasis to bone. BoneKEy Reports 2015; Article number: 643.
[17] T. Stivarou, E. Patsavoudi, Extracellular molecules involved in cancer cell invasion, Cancer (Basel) 7 (1) (2015) 238–265.
[18] P.S. Steeg, Targeting metastasis, Nat. Rev. Cancer 20 (16) (2016) 1–18.
[19] S. Paget, The distribution of secondary growths in cancer of the breast, Cancer Metastasis Rev. 8 (1989) 98–101.
[20] R.R. Langley, I.J. Fidler, The seed and soil hypothesis revisited—the role of tumor-stroma interactions in metastasis to different organs, Int. J. Cancer 128 (11) (2011) 2527–2535.
[21] J. Scott, P. Kuhn, A.R.A. Anderson, Unifying metastasis-integrating intravasation, circulation and end-organ colonization, Nat. Rev. Cancer 12 (7) (2012) 445–446.
[22] N. Syn, L. Wang, G. Sethi, J.P. Thiery, B.C. Goh, Exosome-mediated metastasis: from epithelial-mesenchymal transition to escape from immunosurviellance, Trends Pharmacol. Sci. 37 (7) (2016) 606–617.
[23] C. Scheel, T. Onder, A. Karnoub, R.A. Weinberg, Adaptation versus selection: the origins of metastatic behavior, Cancer Res. 67 (2007) 11476–11479.
[24] C.A. Klein, Parallel progression of primary tumours and metastases, Nat. Rev. Cancer 9 (2009) 302–312.
[25] B.I. Tan, S. Malik, K. Ramnarayanan, J.R. McPharson, D.L. Ho, Y. Suzuki, et al., High-depth sequencing of over 750 genes supports linear progression of primary tumors and metastases in most patients with liver-limited metastatic colorectal cancer, Genome Biol. 16 (2015) 32.
[26] G.S. Mack, A. Marshall, Lost in migration, Nat. Biotechnol. 28 (2010) 214–229.
[27] F. van Zijl, G. Krupitza, W. Mikulits, Initial steps of metastasis: cell invasion and endothelial transmigration, Mutat. Res./Rev. Mutat. Res. 724 (1–2) (2011) 23–34.
[28] N. Tetreault, V. De Guire, miRNAs: their discovery, biogenesis and mechanism of action, Clin. Biochem. 46 (2013) 842–845.
[29] J.T. Parsons, A.R. Horwitz, M.A. Schwartz, Cell adhesion: integrating cytoskeletal dynamics and cellular tension, Nat. Rev. Mol. Cell Biol. 11 (2010) 633–643.
[30] D. Spiering, L. Hodgson, Dynamics of the Rho-family small GTPases in actin regulation and motility, Cell Adh. Migr. 5 (2) (2011) 170–180.
[31] S. Valastyan, F. Reinhardt, N. Benaich, D. Calogrias, A.M. Szasz, Z.C. Wang, et al., A pleiotropically acting microRNA, miR-31, inhibits breast cancer metastasis, Cell 137 (6) (2009) 1032–1046.
[32] C.B. Hu, Q.L. Li, J.F. Hu, Q. Zhang, J.P. Xie, L. Deng, miR-124 inhibits growth and invasion of gastric cancer by targeting ROCK1, Asian Pac. J. Cancer Prev. 15 (16) (2014) 6543–6546.
[33] Z.W. Xi, S.Y. Xin, L.Q. Zhou, H.X. Yuan, Q. Wang, K.X. Chen, Downregulation of rho-associated protein kinase 1 by miR-124 in colorectal cancer, World J. Gastroenterol. 21 (18) (2015) 5454–5464.
[34] S.M. Park, A.B. Gaur, E. Lengyel, M.E. Pete, The miR-200 family determines the epithelial phenotype of cancer cells by targeting the E-cadherin repressors ZEB1 and ZEB2, Genes Dev. 22 (7) (2008) 894–907.
[35] P. Zhang, H. Hong, X. Sun, H. Jiang, S. Ma, S. Zhao, et al., MicroRNA-10b regulates epithelial-mesenchymal transition by modulating KLF4/Notch1/E-cadherin in cisplatin-resistant nasopharyngeal carcinoma cells, Am. J. Cancer. Res. 6 (2) (2016) 141–156.
[36] Y. Song, J. Li, Y. Zhu, Y. Dai, T. Zeng, L. Liu, et al., MicroRNA-9 promotes tumor metastasis via repressing E-cadherin in esophageal squamous cell carcinoma, Oncotarget 5 (22) (2014) 11669–11680.
[37] M.L. Abba, N. Patil, J.H. Leupold, H. Allgayer, MicroRNA regulation of epithelial to mesenchymal transition, J. Clin. Med. 5 (1) (2016) 8.
[38] Rui Zhou, Xiaoshu Zhou, Zhongyuan Yin, Jing Guo, Ting Hu, Shun Jiang, et al., MicroRNA-574-5p promotes metastasis of non-small cell lung cancer by targeting PTPRU, Sci. Rep. 6 (2016) 35714.
[39] R. Takahashi, H. Miyazaki, T. Ochiya, The role of microRNAs in the regulation of cancer stem cells, Front. Genet. 4 (2013) 295.

Please cite this article in press as: M.A. Jafri, et al., Role of miRNAs in human cancer metastasis: Implications for therapeutic intervention, Semin Cancer Biol (2017), http://dx.doi.org/10.1016/j.semcancer.2017.02.004

[40] X. Kong, G. Li, Y. Yuan, Y. He, X. Wu, W. Zhang, et al., MicroRNA-7 Inhibits epithelial-to-mesenchymal transition and metastasis of breast cancer cells via targeting FAK expression, PLoS One 7 (8) (2012) e41523.
[41] R. Matsuyama, D. Okuzaki, M. Okada, C. Oneyama, MicroRNA-27b suppresses tumor progression by regulating ARFGEF1 and focal adhesion signaling, Cancer Sci. 107 (1) (2016) 28–35.
[42] K. Augoff, M. Das, K. Bialkowska, B. McCue, E.F. Plow, K. Sossey-Alaoui, miR-31 is a broad regulator of β1-integrin expression and function in cancer cells, Mol. Cancer Res. 9 (11) (2011) 1500–1508.
[43] B. Yan, Q. Guo, F. Fu, Z. Wang, Z. Yin, Y.B. Wei, et al., The role of miR-29b in cancer: regulation, function and signaling, Onco Targets Ther. 8 (2015) 539–548.
[44] C. Ohyagi-Hara, K. Sawada, S. Kamiura, Y. Tomita, A. Isobe, K. Hashimota, et al., miR-92a inhibits peritoneal dissemination of ovarian cancer cells by inhibiting integrin α5 expression, Am. J. Pathol. 182 (5) (2013) 1876–1889.
[45] Y. Naito, N. Sakamoto, N. Oue, M. Yashiro, K. Sentani, K. Yanagihara, et al., MicroRNA-143 regulates collagen type III expression in stromal fibroblasts of scirrhous type gastric cancer, Cancer Sci. 105 (2) (2014) 228–235.
[46] T. Kinoshita, T. Hanazawa, N. Nohata, N. Kikkawa, H. Enokida, H. Yoshino, et al., Tumor suppressive microRNA-218 inhibits cancer cell migration and invasion through targeting laminin-332 in head and neck squamous cell carcinoma, Oncotarget 3 (11) (2012) 1386–1400.
[47] T. Kinishita, N. Nohata, T. Hanazawa, N. Kikkawa, N. Yamamoto, H. Yoshino, et al., Tumour-suppressive microRNA-29 s inhibit cancer cell migration and invasion by targeting laminin-integrin signalling in head and neck squamous cell carcinoma, Br. J. Cancer 109 (10) (2013) 2636–2645.
[48] S.W. Shan, D.Y. Lee, Z. Deng, T. Shatseva, Z. Jeyapalan, W.W. Du, MicroRNA MiR-17 retards tissue growth and represses fibronectin expression, Nat. Cell Biol. 11 (8) (2009) 1031–1038.
[49] L.R. Patel, D.F. Camacho, Y. Shiozawa, K.J. Pienta, R.S. Taichman, Mechanisms of cancer cell metastasis to the bone: a multistep process, Future Oncol. 7 (11) (2011) 1285–1297.
[50] T.R. Cox, D. Bird, A.M. Baker, H.E. Barker, M.W.Y. Ho, G. Lang, et al., LOX-mediated collagen crosslinking is responsible for fibrosis enhanced metastasis, Cancer Res. 73 (6) (2013) 1721–1732.
[51] H. Wang, Y. Zhu, M. Zhao, C. Wu, P. Zhang, L. Tang, et al., miRNA-29c suppresses lung cancer cell adhesion to extracellular matrix and metastasis by targeting integrin β1 and matrix metalloproteinase2 (MMP2), PLoS One 8 (8) (2013) e70192.
[52] R. Nishikawa, T. Chiyomaru, H. Enokida, S. Inoguchi, T. Ishihara, R. Matsushita, et al., Tumour-suppressive microRNA-29s directly regulate LOXL2 expression and inhibit cancer cell migration and invasion in renal cell carcinoma, FEBS Lett. 589 (2015) 2136–2145.
[53] I. Fukumoto, N. Kikkawa, R. Matsushita, M. Kato, A. Kurozumi, N. Nishikawa, et al., Tumor-suppressive microRNAs (miR-26a/b, miR-29a/b/c and miR-218) concertedly suppressed metastasis-promoting LOXL2 in head and neck squamous cell carcinoma, J. Hum. Genet. 61 (2016) 109–118.
[54] K. Mizuno, N. Seki, H. Mataki, R. Matsushita, K. Kamikawaji, T. Kumamoto, et al., Tumor-suppressive microRNA-29 family inhibits cancer cell migration and invasion directly targeting LOXL2 in lung squamous cell carcinoma, Int. J. Oncol. 48 (2016) 450–460.
[55] B. Deng, Lei Qu, J. Li, J. Fang, S. Yang, Z. Cao, et al., MiRNA-211 suppresses cell proliferation, migration and invasion by targeting SPARC in human hepatocellular carcinoma, Sci. Rep. 6 (2016) 26679.
[56] P. Bornstein, Matricellular proteins: an overview, J. Cell Commun. Signal 3 (2009) 163–165.
[57] A. Zaravinos, The regulatory role of microRNAs in EMT and cancer, J. Oncol. 2015 (2015), Article ID865816.
[58] S.A. Mani, W. Guo, M.J. Liano, E.N. Eaton, A. Ayyana, A.Y. Zhou, et al., The epithelial-mesenchymal transition generates cells with properties of stem cells, Cell 133 (2008) 704–715.
[59] N. Herranz, D. Pasini, V.M. Diaz, C. Franci, A. Gutierrez, N. Dave, et al., Polycomb complex 2 is required for E-cadherin repression by the Snail1 transcription factor, Mol. Cell. Biol. 28 (2008) 4772–4781.
[60] J. Comijn, G. Berx, P. Vermassen, K. Verschueren, L. van Grunsven, E. Bruyneel, et al., The two-handed E box binding zinc finger protein SIP1 downregulates E-cadherin and induces invasion, Mol. Cell 7 (2001) 1267–1278.
[61] A. Eger, K. Aigner, S. Sonderegger, B. Dampier, S. Oehler, M. Schreiber, et al., Delta-EF1 is a transcriptional repressor of E-cadherin and regulates epithelial plasticity in breast cancer cells, Oncogene 24 (2005) 2375–2385.
[62] H. Peinado, E. Ballestar, M. Esteller, A. Cano, Snail mediates E-cadherin repression by the recruitment of the Sin3A/histone deacetylase 1 (HDAC1)/HDAC2 complex, Mol. Cell. Biol. 24 (2004) 306–319.
[63] M.A. Nieto, The snail superfamily of zinc-finger transcription factors, Nat. Rev. Mol. Cell Biol. 3 (2002) 155–166.
[64] X. Feng, Z. Wang, R. Fillmore, Y. Xi, MiR-200, a new star miRNA in human cancer, Cancer Lett. 344 (2) (2014) 166–173.
[65] P.A. Gregory, C.P. Braken, E. Smith, A.G. Bert, J.A. Wright, S. Roslan, et al., An autocrine TGF-beta/ZEB/miR-200 signaling network regulates establishment and maintenance of epithelial-mesenchymal transition, Mol. Biol. Cell 22 (10) (2011) 1686–1698.
[66] Y. Harazono, T. Muramatsu, H. Endo, N. Uzawa, T. Kawano, K. Harada, et al., miR-665 is an EMT-suppressive microRNA targeting ZEB1 and TGFBR2, PLoS One 8 (5) (2013) e62757.
[67] F. Guo, D. Cogdell, L. Hu, D. Yang, A.K. Sood, F. Xue, et al., miR-101 suppresses the epithelial-to-mesenchymal transition by targeting ZEB1 and ZEB2 in ovarian carcinoma, Oncol. Rep. 31 (5) (2014) 2021–2028.
[68] S. Yue, L. Wang, H. Zhang, Y. Min, Y. Lou, H. Sun, et al., miR-139-5p suppresses cancer cell migration and invasion through targeting ZEB1 and ZEB2 in GBM, Tumor Biol. 36 (9) (2015) 6741–6749.
[69] P.A. Gregory, A.G. Bert, E.L. Paterson, S.C. Barry, A. Tsykin, G. Farshid, et al., The miR-200 family and miR-205 regulate epithelial to mesenchymal transition by targeting ZEB1 and SIP1, Nat. Cell Biol. 10 (5) (2008) 593–601.
[70] Y.B. Zheng, H.P. Luo, Q. Shi, Z.N. Hao, Y. Ding, Q.S. Wang, et al., Mir-132 inhibits colorectal cancer invasion and metastasis via directly targeting zeb2, World J. Gastroenterol. 20 (2014) 6515–6522.
[71] J. You, Y. Li, N. Fang, B. Liu, L. Zu, R. Chang, et al., Mir-132 suppresses the migration and invasion of lung cancer cells via targeting the emt regulator zeb2, PLoS One 9 (2014) e91827.
[72] X. Liu, C. Wang, Z. Chen, Y. Jin, Y. Wang, A. Kolokythas, et al., Microrna-138 suppresses epithelial-mesenchymal transition in squamous cell carcinoma cell lines, Biochem. J 440 (2011) 23–31.
[73] R. Tang, L. Liang, D. Luo, Z. Feng, Q. Huang, R. He, et al., Deregulation of miR-30a is associated with poor prognosis in lung cancer, Med. Sci. Monit. 21 (2015) 2514–2520.
[74] R. Kumarswamy, G. Mudduluru, P. Ceppi, S. Muppala, M. Kozlowski, J. Niklinski, et al., MicroRNA-30a inhibits epithelial-to-mesenchymal transition by targeting Snai1 and is downregulated in non-small cell lung cancer, Int. J. Cancer 130 (9) (2012) 2044–2053.
[75] N.H. Kim, H.S. Kim, X.Y. Li, I. Lee, H.S. Choi, S.E. Kang, et al., A p53/miRNA-34 axis regulates Snail1-dependent cancer cell epithelial-mesenchymal transition, J. Cell Biol. 195 (2011) 417–433.
[76] X. Ding, S.I. Park, McCauley, C.Y. Wang, Signaling between transforming growth factor β (TGF-β) and transcription factor SNAI2 represses expression of microRNA miR-203 to promote epithelial-mesenchymal transition and tumor metastasis, J. Biol. Chem. 288 (15) (2013) 10241–10253.
[77] J.O. Yoo, S.Y. Kwak, H.J. An, I.H. Bae, M.J. Park, Y.H. Han, miR-181b-3p promotes epithelial-mesenchymal transition in breast cancer cells through Snail stabilization by directly targeting YWHAG, Biochem. Biophys. Acta 1863 (2016) 1601–1611.
[78] X. Zhu, H. Shen, X. Yin, L. Long, C. Xie, Y. Liu, et al., miR-186 regulation of Twist1 and ovarian cancer sensitivity to cisplatin, Oncogene 35 (3) (2016) 323–332.
[79] K. Sekhon, N. Bucay, S. Majid, R. Dahiya, S. Saini, MicroRNAs and epithelial-mesenchymal transition in prostate cancer, Oncotarget 7 (14) (2016) 67597–67611.
[80] X. Guo, J. Zhang, J. Pang, S. He, G. Li, Y. Chong, et al., MicroRNA-503 represses epithelial–mesenchymal transition and inhibits metastasis of osteosarcoma by targeting c-myb, Tumor Biol. 37 (2016) 9181–9187.
[81] S. Chen, X. Chen, K.-X. Sun, Y.-L. Xiu, B.L. Liu, M.-X. Feng, et al., MicroRNA-93 promotes epithelial–mesenchymal transition of endometrial carcinoma cells, PLoS One 11 (11) (2016) e0165776.
[82] S.Y. Kwak, J.O. Yoo, H.J. An, I.H. Bae, M.J. Park, J. Kim, et al., miR-5003-3p promotes epithelial-mesenchymal transition in breast cancer cells through Snail stabilization and direct targeting of E-cadherin, J. Mol. Cell Biol. 8 (5) (2016) 372–383.
[83] P. Bu, L. Wang, K.Y. Chen, N. Rakhilin, J. Sun, A. Closa, et al., miR-1269 promotes metastasis and forms a positive feedback loop with TGF-β, Nat. Commun. 6 (2015) 6879.
[84] A. Ahmad, S.H. Sarkar, B. Bitar, S. Ali, A. Aboukameel, S. Sethi, et al., Garcinol regulates EMT and Wnt signaling pathways in vitro and in vivo, leading to anticancer activity against breast cancer cells, Mol. Cancer Ther. 11 (2012) 2193–2201.
[85] J. Cai, H. Guan, L. Fang, Y. Yang, X. Zhu, J. Yuan, et al., MicroRNA-374a activates Wnt/β-catenin signaling to promote breast cancer metastasis, J. Clin. Invest. 123 (2) (2013) 566–579.
[86] E.N. Howe, D.R. Cochrane, J.K. Richer, Targets of miR-200c mediate suppression of cell motility and anoikis resistance, Breast Cancer Res. 13 (2) (2011) R45.
[87] S. Jurmeister, M. Baumamm, A. Balwierz, J. Keklikoglou, A. Ward, S. Uhlmann, et al., MicroRNA-200c represses migration and invasion of Breast cancer cells by targeting actin-regulatory proteins FHOD1 and PPM1F, Mol. Cell. Biol. 32 (3) (2012) 633–651.
[88] H. Xu, D. Fei, S. Zong, Z. Fa, MicroRNA-154 inhibits growth and invasion of breast cancer cells through targeting E2F5, Am. J. Transl. Res. 8 (6) (2016) 2620–2630.
[89] S. Mohammadi-Yeganeh, M. Paryan, E. Arefian, M. Vasei, H. Ghanbarian, R. Mahdian, et al., MicroRNA-340 inhibits the migration, invasion, and metastasis of breast cancer cells by targeting Wnt pathway, Tumor Biol. 37 (7) (2016) 8993–9000.
[90] W.Y. Tao, C.H. Wang, Y.H. Sun, Y.H. Su, D. Da Pang, G.Q. Zhang, MicroRNA-34c suppresses breast cancer migration and invasion by targeting GIT1, J. Cancer 7 (12) (2016) 1653–1662.
[91] A. Gilam, J. Conde, D. Weissglas-Volkov, N. Oliva, E. Friedman, N. Natalie Artzi, et al., Local microRNA delivery targets palladin and prevents metastatic breast cancer, Nat. Commun. 7 (2016) 12868.
[92] Y. Hong, H. Liang, U. Rehman, Y. Wang, W. Zhang, Y. Yong Zhou, et al., miR-96 promotes cell proliferation, migration and invasion by targeting PTPN9 in breast cancer, Sci. Rep. 6 (2016) 37421.

Please cite this article in press as: M.A. Jafri, et al., Role of miRNAs in human cancer metastasis: Implications for therapeutic intervention, Semin Cancer Biol (2017), http://dx.doi.org/10.1016/j.semcancer.2017.02.004

[93] T.H. Wang, C.T. Yeh, J.Y. Ho, K.F. Ng, T.C. Chen, OncomiR miR-96 and miR-182 promote cell proliferation and invasion through targeting ephrinA5 in hepatocellular carcinoma, Mol. Carcinog. 55 (4) (2016) 366–375.
[94] M.C. Chu, F.B. Selam, H.S. Taylor, HOXA10 regulates p53 expression and matrigel invasion in human breast cancer cells, Cancer Biol. Ther. 3 (2004) 568–572.
[95] Y. Cheng, J. Zhang, H. Wang, J. Zhao, C. Xu, Y. Du, et al., miRNA-135a promotes breast cancer cell migration and invasion by targeting *HOXA10*, BMC Cancer 12 (2012) 111.
[96] Y.B. Zeng, X.H. Liang, G.X. Zhang, N. Jiang, T. Zhang, J.H. Huanh, et al., miRNA-135a promotes hepatocellular carcinoma cell migration and invasion by targeting forkhead box O1, Cancer Cell Int. 16 (2016) 63.
[97] L. Wu, C. Cai, X. Wang, M. Liu, X. Li, H. Tang, MicroRNA-142-3p a new regulator of RAC1, suppresses the migration and invasion of hepatocellular carcinoma cells, FEBS Lett. 585 (9) (2011) 1322–1330.
[98] L. Qin, Y. Zhang, J. Lin, Y. Shentu, X. Xie, MicroRNA-455 regulates migration and invasion of human hepatocellular carcinoma by targeting Runx2, Oncol. Rep. 36 (6) (2016) 3325–3332.
[99] H. Kayed, X. Jiang, S. Keleg, R. Jesnowski, T. Giese, M.R. Berger, et al., Regulation and functional role of the runt-related transcription factor-2 in pancreatic cancer, Br. J. Cancer 97 (8) (2007) 1106–1115.
[100] J. Wu, G. Wu, L. Lv, Y.F. Ren, X.J. Zhang, Y.F. Xue, et al., MicroRNA-34a inhibits migration and invasion of colon cancer cells via targeting to Fra-1, Carcinogenesis 33 (3) (2012) 519–528.
[101] Yu Zhang, Z. Wang, Min Chen, L. Peng, X. Wang, Q. Ma, et al., MicroRNA-143 targets MACC1 to inhibit cell invasion and migration in colorectal cancer, Mol. Cancer 11 (2012) 23.
[102] B. Deng, B. Wang, J. Fang, X. Zhu, Z. Cao, Q. Lin, et al., MiRNA-203 suppresses cell proliferation, migration and invasion in colorectal cancer via targeting of EIF5A2, Sci. Rep. 6 (2016) 28301.
[103] F.W. Wang, X.Y. Guan, D. Xie, Roles of eukaryotic initiation factor 5A2 in human cancer, Int. J. Biol. Sci. 9 (2013) 1013.
[104] C. Zhou, G. Liu, L. Wang, Y. Lu, L. Yuan, L. Zheng, et al., MiR-339-5p regulates the growth, colony formation and metastasis of colorectal cancer cells by targeting PRL-1, PLoS One 8 (5) (2013) e63142.
[105] C.R. Lima, M.V. Geraldo, C.S. Fuziwara, E.T. Kimura, M.F. Santos, MiRNA-146b-5p upregulates migration and invasion of different papillary thyroid carcinoma cells, BMC Cancer 16 (2016) 108.
[106] Y. Li, L. Wen, Y. Wang, T. Zhou, N. Ma, Z. Hou, MicroRNA-520c enhances cell proliferation, migration, and invasion by suppressing IRF2 in gastric cancer, FEBS Open Biol. 6 (12) (2016) 1257–1266.
[107] X. Zhang, D. Cai, L. Meng, B. Wang, MicroRNA-124 inhibits proliferation, invasion, migration and epithelial-mesenchymal transition of cervical carcinoma cells by targeting astrocyte-elevated gene-1, Oncol. Rep. 36 (4) (2016) 2321–2328.
[108] X.X. He, Y. Chang, F.Y. Meng, M.Y. Wang, Q.H. Xie, F. Tang, et al., MicroRNA-375 targets AEG-1 in hepatocellular carcinoma and suppresses liver cancer cell growth in vitro and in vivo, Oncogene 31 (28) (2012) 3357–3369.
[109] Z. Jiang, Q. Song, R. Zeng, J. Li, J. Li, X. Lin, et al., MicroRNA-218 inhibits EMT, migration and invasion by targeting SFMBT1 and DCUN1D1 in cervical cancer, Oncotarget 7 (29) (2016) 45622–45636.
[110] B. Wang, J. Yang, B. Xiao, MicroRNA-20b (miR-20b) promotes the proliferation, migration, invasion, and tumorigenicity in esophageal cancer cells via the regulation of phosphatase and tensin homologue expression, PLoS One 11 (10) (2016) e0164105.
[111] T. Liang, Y. Cheng, C. Ren, G. Zhang, MicroRNA-194 promotes the growth, migration, and invasion of ovarian carcinoma cells by targeting protein tyrosine phosphatase nonreceptor type 12, Onco Targets Ther. 9 (2016) 4307–4315.
[112] Y. Zheng, C. Zhu, L. Ma, P. Shao, C. Qin, P. Li, et al., miRNA-154-5p Inhibits proliferation, migration and invasion by targeting E2F5 in prostate cancer cell lines, Urol. Int. 98 (1) (2016) 102–110.
[113] Y. Hou, J. Zhen, X. Xu, K. Zhen, B. Zhu, R. Pan, et al., miR-215 functions as a tumor suppressor and directly targets ZEB2 in human non-small cell lung cancer, Oncol. Lett. 10 (2015) 1985–1992.
[114] M. Kato, A. Kurozumi, Y. Goto, R. Matsushita, A. Okato, R. Nishikawa, et al., Regulation of metastasis-promoting LOXL2 gene expression by antitumor microRNAs in prostate cancer, J. Hum. Genet. 62 (2017) 123–132.
[115] S.R. Tie, D.J. McCarthy, T.S. Kendrick, A. Louw, J. Satiaputra, N. Kucera, et al., Regulation of sarcoma cell migration, invasion and invadopodia formation by AFAP1L1 through a phosphotyrosine-dependent pathway, Oncogene 35 (16) (2016) 2098–2111.
[116] B. Jiang, W. Mu, J. Wang, J. Lu, S. Jiang, L. Li, et al., MicroRNA-138 functions as a tumor suppressor in osteosarcoma by targeting differentiated embryonic chondrocyte gene 2, J. Exp. Clin. Cancer Res. 35 (2016) 69.
[117] M. Sachdeva, J.K. Mito, C.L. Lee, M. Zhang, Z. Li, R.d. Dodd, et al., MicroRNA-182 drives metastasis of primary sarcomas by targeting multiple genes, J. Clin. Invest. 124 (10) (2014) 4305–4319.
[118] M. Sachdeva, M.J. Whitley, J.K. Mito, Y. Ma, D.C. Lev, D.M. Cardona, et al., MicroRNA-16 suppresses metastasis in an orthotopic: but not autochthonous, mouse model of soft tissue sarcoma, Dis. Model. Mech. 8 (8) (2015) 867–875.
[119] X. Liu, D. Fan, The epithelial-mesenchymal transition and cancer stem cells: functional and mechanistic links, Curr. Pharm. Des. 21 (2015) 1279–1291.
[120] J. Manuel Iglesias, I. Beloqui, F. Garcia-Garcia, O. Leis, A. Vazquez Martin, A. Eguiara, et al., Mammosphere formation in breast carcinoma cell lines depends upon expression of E-cadherin, PLoS One 8 (10) (2013) e77281.
[121] J.E. Visvader, G.J. Lindeman, Cancer stem cells: current status and evolving complexities, Cell Stem Cell 10 (2012) 717–728.
[122] A.P. Morel, M. Lièvre, C. Thomas, G. Hinkal, S. Ansieau, A. Puisieux, Generation of breast cancer stem cells through epithelial-mesenchymal transition, PLoS One 3 (8) (2008) e2888.
[123] D. Kong, S. Banerjee, A. Ahmad, Y. Li, Z. Wang, S. Sethi, et al., Epithelial to mesenchymal transition is mechanistically linked with stem cell signatures in prostate cancer cells, PLoS One 5 (8) (2010) e12445.
[124] G.J. Klarmann, E.M. Hurt, L.A. Mathews, X. Zhang, M.A. Duhagon, T. Mistree, et al., Invasive prostate cancer cells are tumor initiating cells that have a stem cell-like genomic signature, Clin. Exp. Metastasis 26 (5) (2009) 433–446.
[125] C. Liu, R. Liu, D. Zhang, Q. Deng, B. Liu, H.P. Chao, et al., MicroRNA-141 suppresses prostate cancer stem cells and metastasis by targeting a cohort of pro-metastasis genes, Nat. Commun. 8 (2017) 14270.
[126] C. Morata-Tarifa, G. Jiménez, M.A. García, J.M. Entrena, C. Griñán-Lisón, et al., Low adherent cancer cell subpopulations are enriched in tumorigenic and metastatic epithelial-to-mesenchymal transition-induced cancer stem-like cells, Sci. Rep. 6 (2016) 18772.
[127] Y. Lin, A.Y. Liu, C. Fan, H. Zheng, Y. Li, C. Zhang, et al., MicroRNA-33b inhibits breast cancer metastasis by targeting HMGA2, SALL4 and Twist1, Sci. Rep. 5 (2015) 9995.
[128] B.G. Cuiffo, A. Campagne, G.W. Bell, A. Lembo, F. Orso, E.C. Lien, et al., MSC-regulated microRNAs converge on the transcription factor FOXP2 and promote breast cancer metastasis, Cell Stem Cell 15 (2014) 762–774.
[129] B. Wang, Q. Wang, Z. Wang, J. Jiang, S.C. Yu, Y.F. Ping, et al., Metastatic consequences of immune escape from NK cell cytotoxicity by human breast cancer stem cells, Cancer Res. 74 (2014) 5746–5757.
[130] Y. Shimono, J. Mukohyama, S.I. Nakamura, H. Minami, MicroRNA regulation of human breast cancer stem cells, J. Clin. Med. 5 (1) (2016) 2.
[131] S. Bimonte, A. Barbieri, M. Leongito, G. Palma, V. del Vecchio, M. Falco, et al., The role of miRNAs in the regulation of pancreatic cancer stem cells, Stem Cells Int. 2016 (2016), Article ID 8352684.
[132] A. Ahmed, S. Ali, P.A. Philip, F.H. Sarkar, The role of cancer stem cells and microRNAs in the development and progression of pancreatic cancer, J. Stem Cell Res. Ther. (2012) S7.
[133] R. Sato, T. Semba, H. Saya, Y. Arima, Concise review: stem cells and epithelial-mesenchymal transition in cancer: biological implications and therapeutic targets, Stem Cells 34 (2016) 1997–2007.
[134] W. Zhou, M.Y. Fong, Y. Min, G. Somlo, L. Liu, M.R. Palomares, et al., Cancer-secreted miR-105 destroys vascular endothelial barriers to promote metastasis, Cancer Cell 25 (4) (2014) 501–515.
[135] I.A. Asangani, S.A. Rasheed, D.A. Nikolova, J.H. Leupold, N.H. Colburn, S. Post, et al., MicroRNA-21 (miR-21) post-transcriptionally downregulates tumor suppressor Pdcd4 and stimulates invasion, intravasation and metastasis in colorectal cancer, Oncogene 27 (15) (2008) 2128–2136.
[136] S. Scholch, S.A. Garcia, T. Niemietz, A.M. Betzler, L.K. Nanduri, U. Boek, et al., Circulating tumor cells exhibit stem cell characteristics in an orthopic mouse model of colorectal cancer, Oncotarget 7 (19) (2016) 7232–7242.
[137] A.S. Azevedo, G. Follain, S. Patthabhiraman, S. Harlepp, J.G. Goetz, Metastasis of circulating tumor cells: favorable soil or suitable biomechanics, or both? Cell Adhes. Migr. 9 (5) (2015) 345–356.
[138] X. Liu, Q. Chen, J. Yan, Y. Wang, C. Zhu, C. Chen, et al., MiRNA-296-3p-ICAM-1 axis promotes metastasis of prostate cancer by possible enhancing survival of natural killer cell-resistant circulating tumour cells, Cell Death Dis. 4 (2013) e928.
[139] A. Markou, M. Zavridou, I. Sourvinou, G. Yousef, S. Kounelis, N. Malamos, et al., Direct comparison of metastasis related miRNAs expression levels in circulating tumor cells, corresponding plasma and primary tumors of breast cancer patients, Clin. Chem. 62 (7) (2016) 1002–1011.
[140] N. Reymond, B.B. d'Agua, A.J. Ridley, Crossing the endothelial barrier during metastasis, Nat. Rev. Cancer 13 (2013) 858–870.
[141] J. Massague, A.C. Obenauf, Metastatic colonization by circulating tumour cells, Nature 529 (2016) 298–306.
[142] F. Orso, L. Quirico, F. Virga, E. Penna, D. Dettori, D. Cimino, et al., miR-214 and miR-148b targeting inhibits dissemination of melanoma and breast cancer, Cancer Res. 76 (17) (2016) 1–12.
[143] Q. Chen, X.H.-F. Zhang, J. Massague, Macrophage binding to receptor VCAM-1 transmits survival signals in breast cancer cells that invade the lungs, Cancer Cell 20 (2011) 538–549.
[144] D.X. Nguyen, P.D. Bos, J. Massague, Metastasis: from dissemination to organ-specific colonization, Nat. Rev. Cancer 9 (2009) 274–284.
[145] M. Ono, N. Kosaka, N. Tominaga, Y. Yoshioka, F. Takeshita, R.U. Takahashi, Exosomes from bone marrow mesenchymal stem cells contain a microRNA that promotes dormancy in metastatic breast cancer cells, Sci. Signal. 7 (332) (2014) ra63.
[146] B. De Craene, G. Berx, Regulatory networks defining EMT during cancer initiation and progression, Nat. Rev. Cancer 13 (2) (2013) 97–110.
[147] M.L. Squadrito, F. Pucci, L. Magri, D. Moi, G.D. Gilfillan, A. Ranghetti, miR-511-3p modulates genetic programs of tumor-associated macrophages, Cell Rep. 1 (2) (2012) 141–154.

Please cite this article in press as: M.A. Jafri, et al., Role of miRNAs in human cancer metastasis: Implications for therapeutic intervention, Semin Cancer Biol (2017), http://dx.doi.org/10.1016/j.semcancer.2017.02.004

[148] A.K. Mitra, M. Zillhardt, Y. Hua, P. Tiwari, A.E. Murmann, M.E. Peter, MicroRNAs reprogram normal fibroblasts into cancer-associated fibroblasts in ovarian cancer, Cancer Discov. 2 (12) (2012) 1100–1108.
[149] H.K. Gan, A.N. Cvrljevic, T.G. Johns, The epidermal growth factor receptor variant III (EGFRvIII): where wild things are altered, FEBS J. 280 (2013) 5350–5370.
[150] V. Luga, L. Zhang, A.M. Viloria-Petit, A.A. Ogunjimi, M.R. Inanlou, E. Chiu, et al., Exosomes mediate stromal mobilization of autocrine Wnt-PCP signaling in breast cancer cell migration, Cell 151 (2012) 1542–1556.
[151] A. Thind, C. Wilson, Exosomal miRNAs as cancer biomarkers and therapeutic targets, J. Extracell. Vesicles 5 (2016) 31292.
[152] C.A. Sanchez, E.I. Andahur, R. Valenzuela, E.A. Castellon, J.A. Fulla, C.G. Ramos, et al., Exosomes from bulk and stem cells from human prostate cancer have a differential microRNA content that contributes cooperatively over local and pre-metastatic niche, Oncotarget 7 (2016) 3993–4008.
[153] L. Gwendal, L. Paula, Recent discoveries concerning the tumor-mesenchymal stem cell interactions, Biochim. Biophys. 1866 (2016) 290–299.
[154] F. Gao, Z.L. Zhao, W.T. Zhao, Q.R. Fan, S.C. Wang, J. Li, et al., miR-9 modulates the expression of interferon-regulated genes and MHC class I molecules in human nasopharyngeal carcinoma cells, Biochem. Biophys. Res. Commun. 431 (2013) 610–616.
[155] E. Mogilyansky, I. Rigoutsos, The miR-17/92 cluster: a comprehensive update on its genomics, genetics, functions and increasingly important and numerous roles in health and disease, Cell Death Differ. 20 (2013) 1603–1614.
[156] E. Bell, M.A. Taylor, Functional roles for exosomal microRNAs in the tumour microenvironment, Comput. Struct. Biotechnol. J. 15 (2017) 8–13.
[157] X. Zhang, X. Yuan, H. Shi, L. Wu, H. Qian, W. Xu, Exosomes in cancer: small particles, big player, J. Hematol. Oncol. 8 (2015) 83.
[158] I. Lokody, Exosomally derived miR-105 destroys tight junctions, Nat. Rev. Gen. 15 (2014) 362.
[159] Mirna Therapeutics, Clinical trials and pipeline-MRX34 [cited 2016 Feb 10]. Austin, TX: MirnaTherapeutics; 2015. Available at: http://www.mirnatherapeutics.com/pipeline/mirna-MRX34.html92.
[160] P. Trang, F.G. Wiggins, C.L. Daige, C. Cho, M. Omotola, D. Brown, et al., Systemic delivery of tumor suppressor microRNA mimics using a neutral lipid emulsion inhibits lung tumors in mice, Mol. Ther. 19 (6) (2011) 1116–1122.
[161] L. Zhang, A.K. Iyer, X. Yang, E. Kobayashi, Y. Guo, H. Mankin, et al., Polymeric nanoparticle-based delivery of microRNA-199a-3p inhibits proliferation and growth of osteosarcoma cells, Int. J. Nanomed. 10 (2015) 2913–2924.
[162] Y. Zhang, Z. Wang, R.A. Gemeinhart, Progress in microRNA delivery, J. Control. Release 172 (2013) 962–974.
[163] V. Baumann, J. Winker, miRNA-based therapies: strategies and delivery platforms for oligonucleotide and non-oligonucleotide agents, Future Med. Chem. 6 (17) (2014) 1967–1984.
[164] C.J. Cheng, R. Bahal, I.A. Baber, Z. Pincus, F. Barrera, C. Liu, et al., MicroRNA silencing for cancer therapy targeted to the tumor microenvironment, Nature 518 (7537) (2015) 107–110.
[165] L. Zhou, F. Liu, X. Wang, G. Ouyang, The roles of microRNAs in the regulation of tumor metastasis, Cell Biosci. 5 (2015) 32.
[166] M. Takaishi, M. Tarutani, J. Takeda, S. Sano, Mesenchymal to epithelial transition induced by reprogramming factors attenuates the malignancy of cancer cells, PLoS One 11 (6) (2016) e0156904.
[167] S. Sarkar, H. Dubaybo, S. Ali, P. Goncalves, S.L. Kollepara, S. Sethi, et al., Down-regulation of miR-221 inhibits proliferation of pancreatic cancer cells through up-regulation of PTEN, $p27^{kip1}$, $p57^{kip2}$, and PUMA, Am. J. Cancer Res. 3 (5) (2013) 465–477.
[168] B. Xiong, Y. Cheng, L. Ma, C. Zhang, MiR-21 regulates biological behavior through the PTEN/PI-3K/Akt signaling pathway in human colorectal cancer cells, Int. J. Oncol. 42 (1) (2013) 219–228.
[169] L.Z. Liu, C. Li, Q. Chen, Y. Jing, R. Carpenter, Y. Jiang, et al., MiR-21 induced angiogenesis through AKT and ERK activation and HIF-1α expression, PLoS One 6 (4) (2011) e19139.
[170] A. Zhou, M.Y. Fong, Y. Min, G. Somlo, L. Liu, M.R. Palomares, et al., Cancer-secreted miR-105 destroys vascular endothelial barriers to promote metastasis, Cancer Cell 25 (2014) 501–515.
[171] M. Yang, J. Chen, F. Su, B. Yu, L. Su, L. Lin, et al., Microvesicles secreted by macrophages shuttle invasion-promoting microRNAs into breast cancer cells, Mol. Cancer 10 (2011) 117.
[172] G. Falcone, A. Felsani, I. D'Agnano, Signaling by exosomal microRNAs in cancer, J. Exp. Clin. Cancer Res. 34 (2015) 32.
[173] M.T. Le, P. Hamar, C. Guo, E. Basar, R. Perdigao-Henriques, L. Balaj, et al., miR-200-containing extracellular vesicles promote breast cancer cell metastasis, J. Clin. Invest. 124 (2014) 5109–5128.
[174] S.B. Zhang, H. Zhang, T.T. Cai, Y.N. Liu, J.J. Ni, J. He, et al., Exosomal miR-24-3p impedes T-cell function by targeting *FGF11* and serves as a potential prognostic biomarker for nasopharyngeal carcinoma, J. Pathol. 240 (3) (2016) 329–340.
[175] G. Mao, Y. Liu, X. Fang, Y. Liu, L. Fang, L. Lin, et al., Tumor-derived microRNA-494 promotes angiogenesis in non-small cell lung cancer, Angiogenesis 18 (2015) 373–382.
[176] Z. Li, T.M. Rana, Therapeutic targeting of miRNAs: current status and future challenges, Nat. Rev. Drug Discov. 13 (2014) 622–638.
[177] W. Wang, Y.P. Luo, miRNAs in breast cancer: oncogene and tumor suppressors with clinical potential, J. Zhejiang Univ. Sci. B 16 (1) (2015) 18–31.
[178] C.W. Lin, T.M. Hong, P.C. Yang, MicroRNA-135b as therapeutic target in cancers, RNR Dis. 1 (2014) e410.
[179] Z. Fu, D.J. Tindall, FOXOs, cancer and regulation of apoptosis, Oncogene 27 (2008) 2312–2319.
[180] S. Mattiske, R.J. Suetani, P.M. Neilsen, D.F. Callen, The oncogenic role of miRNA-155 in breast cancer, Cancer Epidemiol. Biomark. Prev. 21 (8) (2012) 1236–1243.
[181] C.J.D. Wallis, A. Gordanpor, J.S. Bendavid, L. Sugars, R.K. Nam, A. Seth, MiR-182 is associated with growth, migration and invasion in prostate cancer via suppression of FOXO1, J. Cancer 6 (12) (2015) 1295–1305.
[182] L. Ma, F. Reinhardt, E. Pan, J. Soutschek, B. Bhat, E. Marcussion, et al., Therapeutic silencing of miR-10b inhibits metastasis in a mouse mammary tumor model, Nat. Biotechnol. 28 (4) (2010) 341–347.
[183] Y. Li, X. Deng, X. Zeng, X. Peng, The role of miR-148a in cancer, J. Cancer 7 (10) (2016) 1233–1241.
[184] Z.H. Tao, J.L. Wan, L.Y. Zeng, L. Xie, H.C. Sun, L.X. Qin, et al., miR-612 suppresses the invasive-metastatic cascade in hepatocellular carcinoma, J. Exp. Med. 210 (4) (2013) 789–803.
[185] L. Sheng, P. He, X. Yang, M. Zhou, Q. Feng, miR-612 negatively regulates colorectal cancer growth and metastasis by targeting AKT2, Cell Death Dis. 6 (2015) e1808.
[186] H.W.Z. Khella, M. Bakhet, G. Allo, M.A.S. Jewett, A.H. Girgis, A. Latif, et al., miR-192, miR-194 and miR-215: a convergent microRNA network suppressing tumor progression in renal cell carcinoma, Carcinogenesis 0 (2013) 1–9.
[187] Q.Y. Li Na Zhang, J.L. Zou, Z.W. Li, T.T. Tian, B. Dong, et al., miR-215 promotes malignant progression of gastric cancer by targeting RUNX1, Oncotarget 7 (4) (2016) 4817–4828.

Please cite this article in press as: M.A. Jafri, et al., Role of miRNAs in human cancer metastasis: Implications for therapeutic intervention, Semin Cancer Biol (2017), http://dx.doi.org/10.1016/j.semcancer.2017.02.004