MicroRNAs in Cancer

Jianzhong Jeff Xi

Abstract

MicroRNAs (miRNAs) are a group of endogenous, small noncoding RNAs of approximately 22 nucleotides in lengths. As a new class of signaling modulators, miRNAs have attracted great attention for their unique features, including multitarget regulation, tissue specificity, and evolutionary conservation. These small endogenous RNAs are able to interact with many important genes and play critical roles in a wide range of biological processes, including cell proliferation and differentiation. Strikingly, miRNAs are frequently dysregulated in human cancers. A number of studies have shown that miRNAs are involved in cancer pathogenesis by regulating oncogenes or tumor suppressor genes. Here, we review recent studies of miRNAs in cancer development and discuss their potential applications in cancer therapeutics.

Keywords

miRNA · microRNA · Global dysregulation · Noncoding RNA · Cancer therapeutics · Diagnostic marker

Contents

J. J. Xi (✉)
Department of Biomedical Engineering, College of Engineering,
Peking University, Beijing 100871, China
e-mail: jzxi@pku.edu.cn

J. Y. Wu (ed.), *RNA and Cancer*, Cancer Treatment and Research,
DOI: 10.1007/978-3-642-31659-3_5, © Springer-Verlag Berlin Heidelberg 2013

1 Introduction

MicroRNAs (miRNAs) are a group of endogenous, small noncoding RNAs of ~22 nucleotides. The human genome contains at least one thousand of distinct miRNAs, which potentially regulate over 30 % of the transcriptome. So far, a number of evidence shows that miRNAs make significant contribution to the formation and development of tumors, especially metastasis. In this chapter, we will start with the introduction of miRNA biogenesis, and summarize the global dysregulation of miRNAs in cancer, and then explain the roles of miRNAs in metastasis and their interaction with conventional protein modulators in several signaling pathways, and finally discuss the potential of miRNAs in therapeutical applications.

2 Biogenesis of miRNAs

The majority of primary miRNA (pri-miRNA) transcripts are produced by RNA polymerase II [9, 72]. The lengths of these pri-miRNAs vary from a few hundred to thousands of nucleotides with one or more double-stranded regions. Some pri-miRNAs have independent transcriptional units with mono- (e.g. miR-21) or polycistronic miRNA-precursor structure (e.g. the miR-17-92-1 cluster) [8, 45], whereas others locate in the intron (e.g. miR-10b) or extron (e.g. miR-198) of messenger RNAs [8, 106]. These polymerase II-directed pri-miRNAs are post-transcriptionally capped at 5′ end or polyadenylated at 3′ end, respectively. However, recent data indicate that a subset of miRNAs may instead be transcribed by RNA Polymerase III, such as C19MC, one of the largest human miRNA clusters [111]. Expression of individual miRNAs is controlled by transcription factors, such as c-Myc or p53. However, the regulatory mechanism of miRNAs at the transcriptional level remains unclear [22, 46, 96, 135].

Following transcription, the pri-miRNA is cleaved by a complex of Drosha and DGCR8 proteins (also known as Pasha), which contains two double-stranded RNA-binding domains [21, 36, 42, 68, 71]. DGCR8 directly interacts with the pri-miRNA and determines the accurate cleavage site. Then the Drosha finishes the cleavage step. An imperfect stem-loop structure of ~50–70 nt in length is released, containing a hairpin stem, a terminal loop and two single-stranded

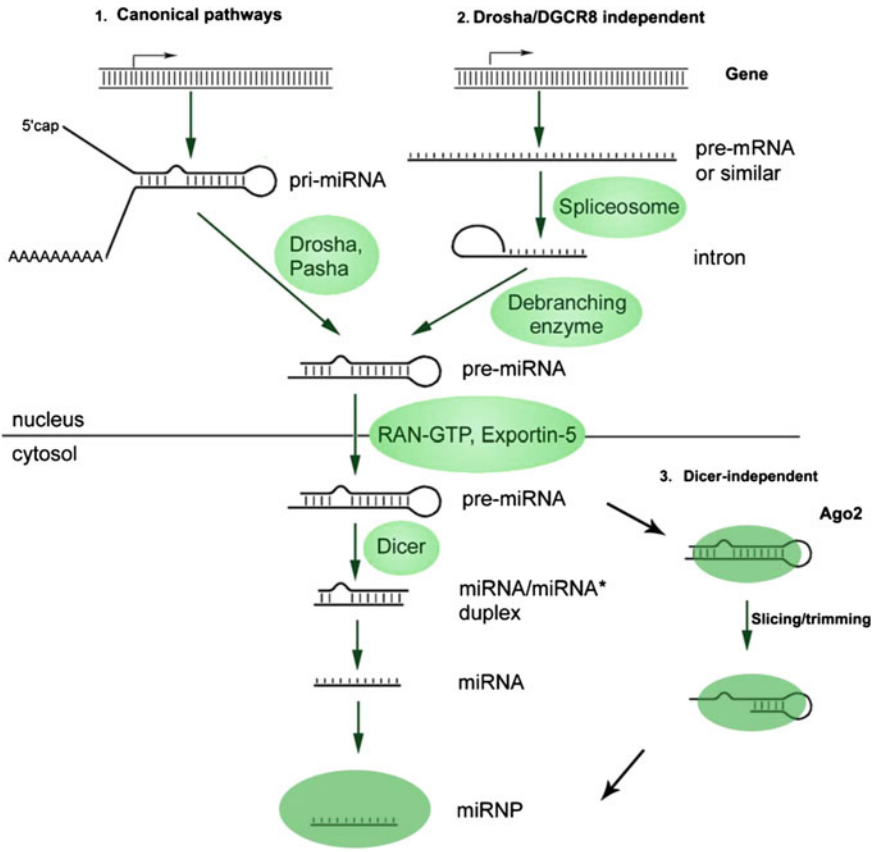

Fig. 1 An illustration of three miRNA biogenesis pathways, including (1) canonical pathway; (2) Drosha/DGCR-independent pathway; or (3) Dicer-independent pathway (adapted from http://en.wikipedia.org/wiki/MicroRNA. With permission from Creative Commons Attribution-ShareAlike 3.0 License)

flanking regions as the precursor miRNA (pre-miRNA). The double-stranded stem and the flanking regions are indispensable for the processing of pre-miRNA, but the loop region is less critical for this step [43, 141, 142].

After processing in the nucleus, the pre-miRNAs are transported to the cytoplasm by the nucleocytoplasmic shuttling protein, exportin-5, which recognizes a two-nucleotide overhang left by Drosha at the 3′ end of the pre-miRNA hairpin. Exportin-5-mediated transport to the cytoplasm is an energy-dependent process, in which GTP is bound to the Ran protein [139]. In the nucleus, in the presence of a high concentration of RanGTP, exportin-5 induces the Drosha/DGCR8 complex to release pre-miRNA and transport pre-miRNA out of the nucleus. In the cytoplasm, the low concentration of RanGTP results in the separation of pre-miRNA from exportin-5. During the subsequent step, another RNase III enzyme, Dicer, cleaves

the loop portion of the hairpin structure and yielding ~22 nt small RNA duplexes, consisting of a mature miRNA strand and a partially complementary strand. Knocking out Dicer blocks the formation of mature miRNAs, indicating that this cleavage is essential for miRNA biogenesis [6, 37, 51, 62]. Dicer cleavage activity is regulated by TRBP, which binds to the amino-terminal DExD/H-box helicase domain of Dicer and induces a conformational rearrangement of Dicer [84].

In addition to the above described canonical miRNA biogenesis pathway, alternative pathways have also been proposed (Fig. 1) [12, 21, 109, 137]. For example, a pre-miRNA-like hairpin structure, which serves as Dicer substrate without cleaving by Drosha/DGCR8 complex, can be generated by many Drosha/DGCR8-independent pathways (e.g. miR-62 or mir-1071) [2, 14, 97, 109]. Another type of miRNAs does not require the cleavage of Dicer. Pri-miR-451 is processed by Drosha/DGCR8 to format a short pre-miRNA with only ~18 nt of duplex stem, which is too short to be recognized by Dicer. Instead, pre-mir-451 is directly cleaved by Ago protein and other proteins [12, 15, 138].

After the miRNA duplex is generated, one strand (named as the guide strand) is loaded into a protein complex called RNA-induced silencing complex (RISC), whereas the other strand gets degraded by cleavage or a bypass mechanism [41]. Argonaute proteins (AGOs) are the catalytic components of the RISC. AGOs have eight related family members in human, including four AGOs and four PIWI proteins. Typically, the mature miRNA-RISC binds to the 3′ untranslated region (3′UTR) of an mRNA containing a partially complementary sequence with the seed region of miRNAs (the 2nd to 8th nt of the mature miRNA). If the seed region of a miRNA can anneal with mRNAs, RISC cleaves these target mRNAs or suppresses their translation without affecting the transcriptional level of these miRNAs.

3 The Dysregulation of miRNAs in Cancer

In 2004, Croce and colleagues reported that miRNAs are not randomly distributed in the human genome [10]. For example, chromosome 4 has fewer than average miRNAs, whereas chromosomes 17 and 19 have significantly more miRNAs. Indeed, over 50 % miRNAs are located at fragile sites or chromosomal regions that are associated with cancers. After systematic analysis of over 200 miRNAs from more than 300 samples, Lu and colleagues revealed distinct expression profiles of miRNAs between normal and tumor cells or tissues [82]. Another interesting finding demonstrated in that work is that miRNA expression profiles can be used to classify poorly differentiated tumors with higher accuracy than mRNA expression files, thus indicating that miRNAs may be used as diagnostic markers.

With the development of high-throughput sequencing technology or gene chip technology, the expression patterns of miRNAs have been intensively investigated in a variety of cells or tissues. A global picture of dysregulation of miRNAs in cancers is emerging, with many miRNAs found down-regulated or overexpressed in different types of tumors. For example, miR-21 or miR-17-92 cluster is up-regulated in a range of tumors [89].

miRNAs may suppress or promote carcinogenesis, acting as either tumor suppressors or oncogenes. Those miRNAs as tumor suppressors are often downregulated in tumors and can regulate oncogenes. For example, let-7 family has been found to negatively regulate expression of RAS, an oncogene that contributes to the pathogenesis of human tumors [56]. Those miRNAs are frequently inactivated either by gene deletion or promoter modification, such as methylation.

Another group of miRNAs, referred to as oncomirs, are found to be overexpressed in cancers. For example, miR-17-92 cluster with six miRNA genes: miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1, and miR-92a-1, can induce cell proliferation, inhibit apoptosis or promote tumorigenesis by cooperating with MYC in lymphomas [33, 96].

miRNAs are also involved in the epigenetic process: either as players or targets in the epigenetic regulation. The methylation of CpG islands in promoter regions leads to silencing of miRNA expression. For example, miR-127, targeting an oncogene-BCL6, is silenced in bladder tumors, but this silence could be rescued using demethylating agents [111]. On the other hand, miRNAs could also regulate enzymes that involves in methylation of CpG islands, such as DNA methyltransferases (DNMT). miR-29 could target DNMT3A and DNMT3B, thus resulting in reactivating p16 tumor suppressor gene [128].

One key question is whether dysregulation of miRNAs is cause or consequence to cancer? [17] Components of the miRNA-machinery have been implicated in tumorigenesis. For example, it was reported that expression of Dicer was downregulated in lung cancer and this downregulation correlated with shortened postoperative survival [57]. In addition, three human Argonaute genes—AGO3, AGO1, and AGO4, which are clustered on chromosome 1 (1p34–35)—are frequently deleted in Wilm's tumor of the kidney and have also been associated with other tumors [24]. In the next section, we will discuss the role or miRNAs in cancer development or metastasis.

4 miRNAs and Cancer Metastasis

Metastases account for 90 % deaths among cancer patients [40]. However, our understanding of the molecular mechanism underlying metastatic dissemination remains obscure [127]. The invasion-metastasis cascade is a dynamic and multistep process. In brief, primary tumor cells break away from neighbouring cells, invade adjacent tissue, enter the circulation systems, extravasate out of the vasculature, seed at distant sites, enter the foreign tissue parenchyma, and finally proliferate from microscopic growths into macroscopic secondary tumors [26]. A large number of studies have showed that miRNAs play a critical role in the initiation and progression of different cancers.

A number of miRNAs act to promote cancer metastasis. For example, miRNA-10b is highly expressed in metastatic breast cancer cells and regulates cell migration and invasion [86]. Overexpression of miR-10b in otherwise non-

metastatic breast tumor cells endows them with invasive and metastatic capability. Significantly, the level of miR-10b expression in primary breast carcinomas correlates with clinical progression. The expression of miR-10b is under the control of Twist, a transcription factor that orchestrates epithelial–mesenchymal transitions (EMT). miR-10b inhibits translation of HOXD10 protein, resulting in the increase of RHOC, a well-characterized prometastatic gene. In addition, miR-373 and miR-520c were identified as another metastasis promoting genes [49]. Overexpression of miR-373 or miR-520c promoted an in vitro migration and invasion of breast cancer cells. miR-373 and miR-520c inhibit CD44, a metastatic suppressor in breast, prostate or colon cancers.

On the other hand, miRNAs can act as inhibitors of metastasis at different stages. Let-7 serves as a tumor suppressor gene by inhibiting the expression of HMGA2 and RAS [56]. Let-7 expression is lower in lung tumors, whereas RAS protein is significantly higher in these tissues. miR-31, another anti-metastatic human miRNA, represses multiple steps of the invasion-metastasis cascade. Down-regulation of miR-31 enhances the migration and invasion in human breast cancer cells. This miRNA can repress a cohort of prometastatic target genes, including Fzd3, ITGA5, MMP16, RDX, and RhoA [88, 110, 113, 127].

Angiogenesis plays a critical role in the tumorigenesis and cancer progression. Vascular endothelial growth factor (VEGF) is a potent proangiogenic factor that is up-regulated in human tumors. miR-126 can directly target the 3′UTRs of Spred-1, VCAM-1, and PIK3R2 [27], negative regulators of VEGF/FGF signaling. In mammals, miR-126 is encoded by intron 7 of the EGF-like domain7 (Egfl7) gene, an endothelial cell-specific secreted peptide that inhibits migration of smooth muscle cell [120]. Thus, miR-126 shows a parallel expression pattern with Egfl7 in tissues or cell lines [28, 99]. Indeed, miR-126 regulates multiple aspects of endothelial cell biology, including cell migration, capillary network stability, and cell survival [27]. Thus, miR-126 promotes VEGF/FGF signaling and angiogenesis by repressing endogenous inhibitors in endothelial cells.

MiR-23b is highly conserved in all vertebrates. Several studies have demonstrated that miR-23b is involved in invasion and metastasis, but the molecular mechanism remains to be elucidated [107, 112]. We have recently demonstrated that miR-23b, which is down-regulated in human colon cancer samples, can potently repress cancer cell migration, invasion, growth, and angiogenesis both in vitro and in vivo [143]. miR-23b can also inhibit VEGF at both transcriptional and translational levels. This miRNA significantly inhibited tubule elongation and branching in vascular formation assay using human umbilical vein endothelial cells (HUVEC). However, miR-23 may regulate angiogenesis by indirectly suppressing VEGF. This miRNA regulates a cohort of prometastatic genes or oncogenes, including FZD7, MAP3K1, PAK2, TGFβR2, RRAS2, or uPA. Re-expression of these individual targets largely reversed effects of miR-23, whereas siRNA silencing of each target genes suppresses metastasis. These six genes participate in critical signaling pathways, including the ERK, JNK, NFκB, PI3K, TGFβ, and Wnt pathways.

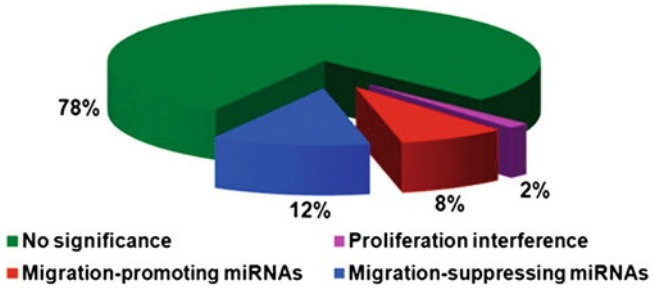

Fig. 2 A pie diagram showing the distribution of miRNAs tested in the migration and proliferation assay (Reprinted from [143]. With permission from Nature Publishing Group)

As described above, miRNAs are frequently dysregulated in human cancers [17, 82]. However, our understanding of role of miRNAs in tumor cell migration remains limited. It is not clear how many miRNAs may affect cancer cell migration, or whether the same miRNA regulates cell migration in different types of cancer cells in a similar manner.

To address these questions, we have systematically investigated regulatory capability of known human miRNAs on cancer cell migration, invasion, or apoptosis [143]. Strikingly, it was found that over one quarter of the human miRNAs tested demonstrated regulatory activities on cancer cell migration (Fig. 2). Interestingly, many of the miRNAs initially identified in a screen in HeLa cells behave in the same manner in four other epithelial cancer cell lines.

Endothelial cell migration plays an important role in the angiogenesis associated with other pathological processes such as atherosclerosis. Thus, we have continued to expand our studies to endothelial cells. It seems that the cell migration regulatory activity of miRNAs is not specific to epithelial cancer cells. It is now well established that miRNAs regulate expression and function of target genes in both physiological and pathological processes. miRNAs modulate many cellular processes including cell migration.

5 miRNAs, Key Modulators in Cell Signaling Pathways

miRNAs play important regulatory roles in a wide range of cellular processes. Individual miRNAs often have multiple target genes. Here, we focus on the roles of miRNAs as modulators in several critical cancer-related signaling pathways, including PI3K/Akt, Erk, MAPK, NF-κB, TGF-β, and mTOR.

5.1 PTEN/PI3K/AKT Signaling Pathway

The PTEN/PI3K/AKT pathway is important in regulating cell proliferation, cellular metabolism, apoptosis, and cell survival. PI3K phosphorylates PIP2 to

Table 1 miRNAs regulating PTEN/PI3 K/AKT signaling pathway

miRNAs	Targets	Effect on AKT pathway	References
miR-126	P85beta	Down	[38]
MiR-7	EGFR	Down	[60]
miR-125b		Down	[74]
miR-184	MicroRNA-205, AKT2	Down	[29, 140]
miR-331-3p	ERBB-2	Down	[23]
miR-8/miR-200	USH/FOG2	Down	[52]
miR-330	E2F1	Down	[70]
miR-320	p85 subunit	Down	[78]
miR-196a	HoxA7, HoxB8, HoxC8 and HoxD8	Up	[116]
miR-146b-5p	EGFR	Down	[58]
miR-149*	Akt1,E2F1	Down	[76]
miR-451	Akt1, CyclinD1, MMP-2, MMP-9 and Bcl-2	Down	[93]
miR-375	PDK1	Down	[124]
miR-222	PPP2R2A	Up	[133]
miR-217	KRAS	Down	[146]
miR-190	PHLPP	Up	[5]
miR-107		Down	[19]
miR-216b	KRAS	Down	[20]
miR-1		Up	[34]
miR-133, miR-223	IGF-1R	Down	[48]
miR-143	ERK5 and/or Akt	Down	[95]
miR-181d	K-ras and Bcl-2	Down	[132]

generate PIP3, an important second messenger, which in turn recruits PDK1 and AKT to the cell membrane. AKT is phosphorylated and activated by PIP3-dependent PDK1, and then regulates many downstream effectors [11]. On the other hand, PTEN dephosphorylates PIP3 to PIP2, thus attenuating the effects of the AKT pathway.

PTEN is a *bona fide* target of miR-21 [90]. Overexpression of miR-21 contributes to hepatocellular carcinoma (HCC) cells and vestibular schwannoma by suppressing PTEN [87, 90]. Interestingly, when PTEN is suppressed by miR-21, AKT induces the down-regulation of miR-199a-5p, leading to increased expression of hypoxia-inducible factor 1alpha (HIF α) and Sirtuin 1 (Sirt1) [114]. This is

one example of miRNAs capable of regulating another miRNA. In addition, PTEN is not only regulated by miR-21, but also by Grhl3, which is a target of miR-21. The interaction of these molecules constitutes a multilayer regulatory network in PTEN/PI3K/AKT pathway [18]. A feed-forward regulatory circuit has been proposed in which miR-21 is a downstream effector of AKT [115].

Many other miRNAs are involved in this pathway through either targeting PTEN or other components. For example, miR-221 and -222 target PTEN as well as TIMP3, leading to the enhancement of TRAIL resistance and cellular migration [32]. miR-221 and -222 are down-regulated by miR-130a [1]. Similar to miR-21, miR-155 may activate AKT pathway via targeting PPP2CA, SOCS1 or SHIP-1 [3, 69]. The miR-17-92 cluster contains six individual miRNAs, among which miR-19 acts as a key component by targeting PTEN [98]. In addition, other miRNAs, including miR-205, 214, 26a, 29a, 29b, 23b, 301, 216a, or 217, can also target PTEN [35, 50, 59, 65, 94, 117, 131, 136] (Table 1).

5.2 MAPK/ERK Signaling Pathway

Mitogen-Activated Protein Kinase (MAPK) or Extracellular signal-Regulated Kinase (ERK) is well-studied protein kinases involved in multiple cellular processes including cell cycle regulation. MAPK/ERK Pathway consists of a series of proteins, which respond to extracellular signals by phosphorylating downstream substrates [64]. Disruption of this pathway leads to cancer and other diseases [63].

MiR-17-5p can target more than 20 genes involved in the G1/S transition in cell cycle, many of which are negative regulators of MAPK signaling cascade [16]. Overall, miR-17-5p promotes the migration of HCC cells through p38 MAPK activation. In addition, miR-17-5 can target E2F1. E2F1-dependent down-regulation of Wip1 is necessary in the activation of p38.

Let-7 family of miRNAs regulates many cellular processes, including cell growth and differentiation [108]. Let-7 reduces the expression of RAS and inhibits the MAPK/ERK pathway in papillary thyroid cancer [104]. In breast cancers, let-7 g plays an antitumor role by reducing p44/42 MAPK [102]. As a modulator of K-RAS, miR-143 decreases the proliferation and migration of prostate cancer cells [134]. Many other miRNAs, including miR-18*, miR-143, miR-181, and miR-622, also target K-RAS [31, 44, 118, 123, 132].

Spred1 is a negative regulator in MAPK/ERK pathway. miR-126 can enhance the proliferation of mast cell by inhibiting spred1 [54]. In mesenchymal stem cells, overexpression of miR-126 enhances ischemic angiogenesis by increasing the protein levels of ERK1, pErk1, AKT, or pAKT [13]. miR-133b can promote the development of cervical carcinoma by targeting MST2, CDC42, or RHOA [103]. In addition to modulating the PTEN/PI3K/AKT pathway, miR-21 regulates Spry1, Spry2, Btg2, and Pdcd4, known negative regulators in the Ras/MEK/ERK pathway. Other miRNAs are capable of regulating downstream effectors in MAPK/ERK pathway, including miR-146 and miR-221/222 [83, 100, 122].

5.3 NF-κB Signaling Pathway

NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) is a protein complex that controls the transcription of many genes. When bound to an inhibitor-IκB, NF-κB is kept inactive in the cytoplasm. When cells are stimulated, an IκB kinase, IKK, is activated to phosphorylate IκB, resulting in the degradation of IκB and the activation of NF-κB. NF-κB then translocates into the nucleus and turns on the expression of its target genes.

The expression of miR-9 can be regulated by the activated NF-κB. On the other hand, miR-9 can affect the expression of NF-κB, forming a feedback regulation [4]. It was also found that NFKB1 was suppressed when miR-9 was overexpressed in ovarian cancer [39]. miR-146 can indirectly suppress NF-κB pathway by targeting IL-1 receptor-associated kinase or TNF receptor-associated factor 6 [7], thereby regulating IL-1 and Toll-like receptor signaling pathways.

Many other miRNAs also participate in the regulation of NF-κB pathway, including miR-98, let-7, miR-21, miR-124, miR-155, miR-15, and -16 [47, 53, 75, 77, 81, 105, 130]. On the other hand, NF-κB signaling pathway controls the expression of many genes, including miR-146, 147, or 143 [79, 121, 144].

5.4 TGF-β and mTOR Pathways

miR-21, miR-133 and 590, miR-17 cluster, miR200a, miR-106b-25 cluster, miR-210, miR-26a, or miR520/373 regulate the effectors in the TGF-β signaling pathway [61, 91, 119, 129]. The key modulators in the mTOR signaling pathway can be regulated by miR-199a-3p, miR-100, miR-221, miR-223, miR-99a, miR-218, miR-7, miR-376b, miR-520c and -373 [25, 30, 55, 66, 73, 80, 92, 101, 125].

From the limited examples described above, it is clear that miRNAs are emerging as a group of important modulators of many signaling pathways important for tumorigenesis and cancer metastasis. In a number of cases, miRNAs and their target genes can form feedback regulatory loops. It is conceivable that disruption of certain critical regulatory networks may contribute to tumor development and progression.

6 Therapeutic Potential for miRNAs

As discussed above, aberrant expression and regulation of miRNA genes have been associated with a wide range of human cancers. A number of miRNAs play critical roles in cancer development and metastasis. Such miRNAs may have great potential in serving as diagnostic biomarkers or therapeutic targets for human cancers. Indeed, several miRNAs have been identified to inhibit cancer metastasis in cellular or animal models. For example, Weinberg and colleagues demonstrated that systemic administration of miR-10b antagomirs, an inhibitor against miR-10b, inhibited breast cancer metastasis in tumor-bearing mice [85]. In another study,

systemic administration of miR-26a in a mouse model of HCC using adeno-associated virus (AAV) results in inhibition of cancer cell proliferation, induction of tumor-specific apoptosis, and dramatic protection from disease progression without obvious toxicity [67]. Their unique features, including multitarget regulation and tissue specificity make miRNAs attractive target genes for developing cancer therapeutics, although much more work is needed to make this a reality.

7 Concluding Remarks

One miRNA may regulate up to hundreds of genes. Accumulating data support that miRNAs behave as buffer molecules capable of tuning the expression of target genes to appropriate levels. Expression of a certain miRNA in tumors is expected to regulate a cohort of functionally relevant genes. Although the target-specific delivery of siRNA/miRNA is still a challenging issue, detections of miRNAs in the serum suggest a new strategy to package or deliver miRNAs into specific cells or tissues [126, 145]. Another challenge is that we still lack a powerful approach to systematically identify the target genes regulated by miRNAs. A deeper understanding of the relationship between miRNAs and their targets is necessary for developing applications of these non-coding RNAs in cancer diagnostics and therapeutics.

Acknowledgments I thank Yang Hao, Junyu Yang, Ming Ma, Mingjun Jiang, Hanshuo Zhang, and Yanzhen Ye for their collecting literature and manuscription preparation. I also thank Dr. Jane Wu for manuscrition editing and discussion. This work was supported by projects of NSFC (Grant No. 81030040), MOST (Grant No. 2008ZX09401—002, 2011CB809106), NSFC (20733001, 30600142), and Coulter Foundation Seed Grant.

References

1. Acunzo M, Visone R, Romano G, Veronese A, Lovat F, Palmieri D, Bottoni A, Garofalo M, Gasparini P, Condorelli G et al (2012) miR-130a targets MET and induces TRAIL-sensitivity in NSCLC by downregulating miR-221 and 222. Oncogene 31:634–642
2. Babiarz JE, Ruby JG, Wang Y, Bartel DP, Blelloch R (2008) Mouse ES cells express endogenous shRNAs, siRNAs, and other microprocessor-independent, dicer-dependent small RNAs. Genes Dev 22:2773–2785
3. Bakirtzi K, Hatziapostolou M, Karagiannides I, Polytarchou C, Jaeger S, Iliopoulos D, Pothoulakis C (2011) Neurotensin signaling activates microRNAs-21 and -155 and Akt, promotes tumor growth in mice, and is increased in human colon tumors. Gastroenterology 141(1749–1761):e1741
4. Bazzoni F, Rossato M, Fabbri M, Gaudiosi D, Mirolo M, Mori L, Tamassia N, Mantovani A, Cassatella MA, Locati M (2009) Induction and regulatory function of miR-9 in human monocytes and neutrophils exposed to proinflammatory signals. Proc Natl Acad Sci U S A 106:5282–5287
5. Beezhold K, Liu J, Kan H, Meighan T, Castranova V, Shi X, Chen F (2011) miR-190-mediated downregulation of PHLPP contributes to arsenic-induced Akt activation and carcinogenesis. Toxicol Sci 123:411–420

6. Bernstein E, Caudy AA, Hammond SM, Hannon GJ (2001) Role for a bidentate ribonuclease in the initiation step of RNA interference. Nature 409:363–366
7. Bhaumik D, Scott GK, Schokrpur S, Patil CK, Campisi J, Benz CC (2008) Expression of microRNA-146 suppresses NF-kappaB activity with reduction of metastatic potential in breast cancer cells. Oncogene 27:5643–5647
8. Borchert GM, Lanier W, Davidson BL (2006) RNA polymerase III transcribes human microRNAs. Nat Struct Mol Biol 13:1097–1101
9. Cai X, Hagedorn CH, Cullen BR (2004) Human microRNAs are processed from capped, polyadenylated transcripts that can also function as mRNAs. RNA 10:1957–1966
10. Calin GA, Sevignani C, Dumitru CD, Hyslop T, Noch E, Yendamuri S, Shimizu M, Rattan S, Bullrich F, Negrini M et al (2004) Human microRNA genes are frequently located at fragile sites and genomic regions involved in cancers. Proc Natl Acad Sci U.S.A 101:2999–3004
11. Carnero A, Blanco-Aparicio C, Renner O, Link W, Leal JF (2008) The PTEN/PI3 K/AKT signaling pathway in cancer, therapeutic implications. Curr Cancer Drug Targets 8:187–198
12. Cheloufi S, Dos Santos CO, Chong MM, Hannon GJ (2010) A dicer-independent miRNA biogenesis pathway that requires Ago catalysis. Nature 465:584–589
13. Chen JJ, Zhou SH (2011) Mesenchymal stem cells overexpressing MiR-126 enhance ischemic angiogenesis via the AKT/ERK-related pathway. Cardiol J 18:675–681
14. Chung WJ, Agius P, Westholm JO, Chen M, Okamura K, Robine N, Leslie CS, Lai EC (2011) Computational and experimental identification of mirtrons in Drosophila melanogaster and Caenorhabditis elegans. Genome Res 21:286–300
15. Cifuentes D, Xue H, Taylor DW, Patnode H, Mishima Y, Cheloufi S, Ma E, Mane S, Hannon GJ, Lawson ND et al (2010) A novel miRNA processing pathway independent of Dicer requires Argonaute2 catalytic activity. Science 328:1694–1698
16. Cloonan N, Brown MK, Steptoe AL, Wani S, Chan WL, Forrest AR, Kolle G, Gabrielli B, Grimmond SM (2008) The miR-17-5p microRNA is a key regulator of the G1/S phase cell cycle transition. Genome Biol 9:R127
17. Croce CM (2009) Causes and consequences of microRNA dysregulation in cancer. Nat Rev Genet 10:704–714
18. Darido C, Georgy SR, Wilanowski T, Dworkin S, Auden A, Zhao Q, Rank G, Srivastava S, Finlay MJ, Papenfuss AT et al (2011) Targeting of the tumor suppressor GRHL3 by a miR-21-dependent proto-oncogenic network results in PTEN loss and tumorigenesis. Cancer Cell 20:635–648
19. Datta J, Smith A, Lang JC, Islam M, Dutt D, Teknos TN, Pan Q (2011) microRNA-107 functions as a candidate tumor-suppressor gene in head and neck squamous cell carcinoma by downregulation of protein kinase Cvarepsilon. Oncogene doi:10.1038/onc.2011.565
20. Deng M, Tang H, Zhou Y, Zhou M, Xiong W, Zheng Y, Ye Q, Zeng X, Liao Q, Guo X et al (2011) miR-216b suppresses tumor growth and invasion by targeting KRAS in nasopharyngeal carcinoma. J Cell Sci 124:2997–3005
21. Denli AM, Tops BB, Plasterk RH, Ketting RF, Hannon GJ (2004) Processing of primary microRNAs by the Microprocessor complex. Nature 432:231–235
22. Diederichs S, Haber DA (2006) Sequence variations of microRNAs in human cancer: alterations in predicted secondary structure do not affect processing. Cancer Res 66:6097–6104
23. Epis MR, Giles KM, Barker A, Kendrick TS, Leedman PJ (2009) miR-331-3p regulates ERBB-2 expression and androgen receptor signaling in prostate cancer. J Biol Chem 284:24696–24704
24. Esquela-Kerscher A, Slack FJ (2006) Oncomirs—microRNAs with a role in cancer. Nat Rev Cancer 6:259–269
25. Fang YX, Xue JL, Shen Q, Chen J, L (2012) miR-7 inhibits tumorgrowth and metastasis by targeting the PI3K/AKT pathway in hepatocellularcarcinoma. Hepatology 55(6):1852–1862
26. Fidler IJ (2003) The pathogenesis of cancer metastasis: the 'seed and soil' hypothesis revisited. Nat Rev Cancer 3:453–458

27. Fish JE, Santoro MM, Morton SU, Yu S, Yeh RF, Wythe JD, Ivey KN, Bruneau BG, Stainier DY, Srivastava D (2008) miR-126 regulates angiogenic signaling and vascular integrity. Dev Cell 15:272–284
28. Fitch MJ, Campagnolo L, Kuhnert F, Stuhlmann H (2004) Egfl7, a novel epidermal growth factor-domain gene expressed in endothelial cells. Dev Dyn 230:316–324
29. Foley NH, Bray IM, Tivnan A, Bryan K, Murphy DM, Buckley PG, Ryan J, O'Meara A, O'Sullivan M, Stallings RL (2010) MicroRNA-184 inhibits neuroblastoma cell survival through targeting the serine/threonine kinase AKT2. Mol Cancer 9:83
30. Fornari F, Milazzo M, Chieco P, Negrini M, Calin GA, Grazi GL, Pollutri D, Croce CM, Bolondi L, Gramantieri L (2010) MiR-199a-3p regulates mTOR and c-Met to influence the doxorubicin sensitivity of human hepatocarcinoma cells. Cancer Res 70:5184–5193
31. Gao JS, Zhang Y, Tang X, Tucker LD, Tarwater PM, Quesenberry PJ, Rigoutsos I, Ramratnam B (2011) The Evi1, microRNA-143, K-Ras axis in colon cancer. FEBS Lett 585:693–699
32. Garofalo M, Di Leva G, Romano G, Nuovo G, Suh SS, Ngankeu A, Taccioli C, Pichiorri F, Alder H, Secchiero P et al (2009) miR-221&222 regulate TRAIL resistance and enhance tumorigenicity through PTEN and TIMP3 downregulation. Cancer Cell 16:498–509
33. Garzon R, Heaphy CE, Havelange V, Fabbri M, Volinia S, Tsao T, Zanesi N, Kornblau SM, Marcucci G, Calin GA et al (2009) MicroRNA 29b functions in acute myeloid leukemia. Blood 114:5331–5341
34. Glass C, Singla DK (2011) MicroRNA-1 transfected embryonic stem cells enhance cardiac myocyte differentiation and inhibit apoptosis by modulating the PTEN/Akt pathway in the infarcted heart. Am J Physiol Heart Circ Physiol 301:2038–2049
35. Greene SB, Gunaratne PH, Hammond SM, Rosen JM (2010) A putative role for microRNA-205 in mammary epithelial cell progenitors. J Cell Sci 123:606–618
36. Gregory RI, Yan KP, Amuthan G, Chendrimada T, Doratotaj B, Cooch N, Shiekhattar R (2004) The Microprocessor complex mediates the genesis of microRNAs. Nature 432:235–240
37. Grishok A, Pasquinelli AE, Conte D, Li N, Parrish S, Ha I, Baillie DL, Fire A, Ruvkun G, Mello CC (2001) Genes and mechanisms related to RNA interference regulate expression of the small temporal RNAs that control C. elegans developmental timing. Cell 106:23–34
38. Guo C, Sah JF, Beard L, Willson JK, Markowitz SD, Guda K (2008) The noncoding RNA, miR-126, suppresses the growth of neoplastic cells by targeting phosphatidylinositol 3-kinase signaling and is frequently lost in colon cancers. Genes Chromosomes Cancer 47:939–946
39. Guo LM, Pu Y, Han Z, Liu T, Li YX, Liu M, Li X, Tang H (2009) MicroRNA-9 inhibits ovarian cancer cell growth through regulation of NF-kappaB1. FEBS J 276:5537–5546
40. Gupta GP, Massague J (2006) Cancer metastasis: building a framework. Cell 127:679–695
41. Hammond SM, Bernstein E, Beach D, Hannon GJ (2000) An RNA-directed nuclease mediates post-transcriptional gene silencing in Drosophila cells. Nature 404:293–296
42. Han J, Lee Y, Yeom KH, Kim YK, Jin H, Kim VN (2004) The Drosha-DGCR8 complex in primary microRNA processing. Gene Dev 18:3016–3027
43. Han J, Lee Y, Yeom KH, Nam JW, Heo I, Rhee JK, Sohn SY, Cho Y, Zhang BT, Kim VN (2006) Molecular basis for the recognition of primary microRNAs by the Drosha-DGCR8 complex. Cell 125:887–901
44. Han Z, Yang Q, Liu B, Wu J, Li Y, Yang C, Jiang Y (2012) MicroRNA-622 functions as a tumor suppressor by targeting K-Ras and enhancing the anticarcinogenic effect of resveratrol. Carcinogenesis 33:131–139
45. Hayashita Y, Osada H, Tatematsu Y, Yamada H, Yanagisawa K, Tomida S, Yatabe Y, Kawahara K, Sekido Y, Takahashi T (2005) A polycistronic microRNA cluster, miR-17-92, is overexpressed in human lung cancers and enhances cell proliferation. Cancer Res 65:9628–9632

46. He L, He X, Lim LP, de Stanchina E, Xuan Z, Liang Y, Xue W, Zender L, Magnus J, Ridzon D et al (2007) A microRNA component of the p53 tumor suppressor network. Nature 447:1130–1134
47. Hu G, Zhou R, Liu J, Gong AY, Eischeid AN, Dittman JW, Chen XM (2009) MicroRNA-98 and let-7 confer cholangiocyte expression of cytokine-inducible Src homology 2-containing protein in response to microbial challenge. J Immunol 183:1617–1624
48. Huang MB, Xu H, Xie SJ, Zhou H, Qu LH (2011) Insulin-like growth factor-1 receptor is regulated by microRNA-133 during skeletal myogenesis. PLoS One 6:e29173
49. Huang Q, Gumireddy K, Schrier M, le Sage C, Nagel R, Nair S, Egan DA, Li A, Huang G, Klein-Szanto AJ et al (2008) The microRNAs miR-373 and miR-520c promote tumor invasion and metastasis. Nat Cell Biol 10:202–210
50. Huse JT, Brennan C, Hambardzumyan D, Wee B, Pena J, Rouhanifard SH, Sohn-Lee C, le Sage C, Agami R, Tuschl T et al (2009) The PTEN-regulating microRNA miR-26a is amplified in high-grade glioma and facilitates gliomagenesis in vivo. Gene Dev 23:1327–1337
51. Hutvagner G, McLachlan J, Pasquinelli AE, Balint E, Tuschl T, Zamore PD (2001) A cellular function for the RNA-interference enzyme Dicer in the maturation of the let-7 small temporal RNA. Science 293:834–838
52. Hyun S, Lee JH, Jin H, Nam J, Namkoong B, Lee G, Chung J, Kim VN (2009) Conserved MicroRNA miR-8/miR-200 and its target USH/FOG2 control growth by regulating PI3 K. Cell 139:1096–1108
53. Iliopoulos D, Hirsch HA, Struhl K (2009) An epigenetic switch involving NF-kappaB, Lin28, Let-7 MicroRNA, and IL6 links inflammation to cell transformation. Cell 139:693–706
54. Ishizaki T, Tamiya T, Taniguchi K, Morita R, Kato R, Okamoto F, Saeki K, Nomura M, Nojima Y, Yoshimura A (2011) miR126 positively regulates mast cell proliferation and cytokine production through suppressing Spred1. Genes Cells 16:803–814
55. Jia CY, Li HH, Zhu XC, Dong YW, Fu D, Zhao QL, Wu W, Wu XZ (2011) MiR-223 suppresses cell proliferation by targeting IGF-1R. PLoS One 6:e27008
56. Johnson SM, Grosshans H, Shingara J, Byrom M, Jarvis R, Cheng A, Labourier E, Reinert KL, Brown D, Slack FJ (2005) RAS is regulated by the let-7 microRNA family. Cell 120:635–647
57. Karube Y, Tanaka H, Osada H, Tomida S, Tatematsu Y, Yanagisawa K, Yatabe Y, Takamizawa J, Miyoshi S, Mitsudomi T et al (2005) Reduced expression of Dicer associated with poor prognosis in lung cancer patients. Cancer Sci 96:111–115
58. Katakowski M, Zheng X, Jiang F, Rogers T, Szalad A, Chopp M (2010) MiR-146b-5p suppresses EGFR expression and reduces in vitro migration and invasion of glioma. Cancer Invest 28:1024–1030
59. Kato M, Putta S, Wang M, Yuan H, Lanting L, Nair I, Gunn A, Nakagawa Y, Shimano H, Todorov I et al (2009) TGF-beta activates Akt kinase through a microRNA-dependent amplifying circuit targeting PTEN. Nat Cell Biol 11:881–889
60. Kefas B, Godlewski J, Comeau L, Li Y, Abounader R, Hawkinson M, Lee J, Fine H, Chiocca EA, Lawler S et al (2008) microRNA-7 inhibits the epidermal growth factor receptor and the Akt pathway and is down-regulated in glioblastoma. Cancer Res 68:3566–3572
61. Keklikoglou I, Koerner C, Schmidt C, Zhang JD, Heckmann D, Shavinskaya A, Allgayer H, Guckel B, Fehm T, Schneeweiss A et al (2011) MicroRNA-520/373 family functions as a tumor suppressor in estrogen receptor negative breast cancer by targeting NF-kappaB and TGF-beta signaling pathways. Oncogene
62. Ketting RF, Fischer SE, Bernstein E, Sijen T, Hannon GJ, Plasterk RH (2001) Dicer functions in RNA interference and in synthesis of small RNA involved in developmental timing in C. elegans. Gene Dev 15:2654–2659
63. Khavari TA, Rinn J (2007) Ras/Erk MAPK signaling in epidermal homeostasis and neoplasia. Cell Cycle 6:2928–2931

64. Kolch W (2005) Coordinating ERK/MAPK signaling through scaffolds and inhibitors. Nat Rev Mol Cell Biol 6:827–837
65. Kong G, Zhang J, Zhang S, Shan C, Ye L, Zhang X (2011) Upregulated microRNA-29a by hepatitis B virus X protein enhances hepatoma cell migration by targeting PTEN in cell culture model. PLoS One 6:e19518
66. Korkmaz G, le Sage C, Tekirdag KA, Agami R, Gozuacik D (2012) miR-376b controls starvation and mTOR inhibition-related autophagy by targeting ATG4C and BECN1. Autophagy 8(2):165–176
67. Kota J, Chivukula RR, O'Donnell KA, Wentzel EA, Montgomery CL, Hwang HW, Chang TC, Vivekanandan P, Torbenson M, Clark KR et al (2009) Therapeutic microRNA delivery suppresses tumorigenesis in a murine liver cancer model. Cell 137:1005–1017
68. Landthaler M, Yalcin A, Tuschl T (2004) The human DiGeorge syndrome critical region gene 8 and Its D. melanogaster homolog are required for miRNA biogenesis. Curr Biol 14:2162–2167
69. Lee DW, Futami M, Carroll M, Feng Y, Wang Z, Fernandez M, Whichard Z, Chen Y, Kornblau S, Shpall EJ et al (2012) Loss of SHIP-1 protein expression in high-risk myelodysplastic syndromes is associated with miR-210 and miR-155. Oncogene doi: 10.1038/onc.2011.579
70. Lee KH, Chen YL, Yeh SD, Hsiao M, Lin JT, Goan YG, Lu PJ (2009) MicroRNA-330 acts as tumor suppressor and induces apoptosis of prostate cancer cells through E2F1-mediated suppression of Akt phosphorylation. Oncogene 28:3360–3370
71. Lee Y, Ahn C, Han J, Choi H, Kim J, Yim J, Lee J, Provost P, Radmark O, Kim S et al (2003) The nuclear RNase III Drosha initiates microRNA processing. Nature 425:415–419
72. Lee Y, Kim M, Han J, Yeom KH, Lee S, Baek SH, Kim VN (2004) MicroRNA genes are transcribed by RNA polymerase II. EMBO J 23:4051–4060
73. Li D, Liu X, Lin L, Hou J, Li N, Wang C, Wang P, Zhang Q, Zhang P, Zhou W et al (2011) MicroRNA-99a inhibits hepatocellular carcinoma growth and correlates with prognosis of patients with hepatocellular carcinoma. J Biol Chem 286:36677–36685
74. Li W, Xie L, He X, Li J, Tu K, Wei L, Wu J, Guo Y, Ma X, Zhang P et al (2008) Diagnostic and prognostic implications of microRNAs in human hepatocellular carcinoma. Int J Cancer 123:1616–1622
75. Li Y, Li W, Yang Y, Lu Y, He C, Hu G, Liu H, Chen J, He J, Yu H (2009) MicroRNA-21 targets LRRFIP1 and contributes to VM-26 resistance in glioblastoma multiforme. Brain Res 1286:13–18
76. Lin RJ, Lin YC, Yu AL (2010) miR-149* induces apoptosis by inhibiting Akt1 and E2F1 in human cancer cells. Mol Carcinog 49:719–727
77. Lindenblatt C, Schulze-Osthoff K, Totzke G (2009) IkappaBzeta expression is regulated by miR-124a. Cell Cycle 8:2019–2023
78. Ling HY, Ou HS, Feng SD, Zhang XY, Tuo QH, Chen LX, Zhu BY, Gao ZP,Tang CK, Yin WD et al (2009) Changes in microRNA profile and effects ofmiR-320 in insulin-resistant 3T3-L1 adipocytes. Clin Exp Pharmacol Physiol 36(9):e32–e39
79. Liu G, Friggeri A, Yang Y, Park YJ, Tsuruta Y, Abraham E (2009) miR-147, a microRNA that is induced upon Toll-like receptor stimulation, regulates murine macrophage inflammatory responses. Proc Natl Acad Sci U S A 106:15819–15824
80. Liu P, Wilson MJ (2012) miR-520c and miR-373 upregulate MMP9 expression by targeting mTOR and SIRT1, and activate the Ras/Raf/MEK/Erk signaling pathway and NF-kappaB factor in human fibrosarcoma cells. J Cell Physiol 227:867–876
81. Lu F, Weidmer A, Liu CG, Volinia S, Croce CM, Lieberman PM (2008) Epstein-Barr virus-induced miR-155 attenuates NF-kappaB signaling and stabilizes latent virus persistence. J Virol 82:10436–10443
82. Lu J, Getz G, Miska EA, Alvarez-Saavedra E, Lamb J, Peck D, Sweet-Cordero A, Ebert BL, Mak RH, Ferrando AA et al (2005) MicroRNA expression profiles classify human cancers. Nature 435:834–838

83. Lu Y, Roy S, Nuovo G, Ramaswamy B, Miller T, Shapiro C, Jacob ST, Majumder S (2011) Anti-microRNA-222 (anti-miR-222) and -181B suppress growth of tamoxifen-resistant xenografts in mouse by targeting TIMP3 protein and modulating mitogenic signal. J Biol Chem 286:42292–42302
84. Ma E, MacRae IJ, Kirsch JF, Doudna JA (2008) Autoinhibition of human dicer by its internal helicase domain. J Mol Biol 380:237–243
85. Ma L, Reinhardt F, Pan E, Soutschek J, Bhat B, Marcusson EG, Teruya-Feldstein J, Bell GW, Weinberg RA (2010) Therapeutic silencing of miR-10b inhibits metastasis in a mouse mammary tumor model. Nat Biotechnol 28:341–347
86. Ma L, Teruya-Feldstein J, Weinberg RA (2007) Tumor invasion and metastasis initiated by microRNA-10b in breast cancer. Nature 449:682–688
87. Ma X, Kumar M, Choudhury SN, Becker Buscaglia LE, Barker JR, Kanakamedala K, Liu MF, Li Y (2011) Loss of the miR-21 allele elevates the expression of its target genes and reduces tumorigenesis. In: Proceedings of the National Academy of Sciences of the United States of America, vol 108, pp 10144–10149
88. McClatchey AI (2003) Merlin and ERM proteins: unappreciated roles in cancer development? Nat Rev Cancer 3:877–883
89. Mendell JT (2008) miRiad roles for the miR-17-92 cluster in development and disease. Cell 133:217–222
90. Meng F, Henson R, Wehbe-Janek H, Ghoshal K, Jacob ST, Patel T (2007) MicroRNA-21 regulates expression of the PTEN tumor suppressor gene in human hepatocellular cancer. Gastroenterology 133:647–658
91. Mizuno Y, Tokuzawa Y, Ninomiya Y, Yagi K, Yatsuka-Kanesaki Y, Suda T, Fukuda T, Katagiri T, Kondoh Y, Amemiya T et al (2009) miR-210 promotes osteoblastic differentiation through inhibition of AcvR1b. FEBS Lett 583:2263–2268
92. Nagaraja AK, Creighton CJ, Yu Z, Zhu H, Gunaratne PH, Reid JG, Olokpa E, Itamochi H, Ueno NT, Hawkins SM et al (2010) A link between mir-100 and FRAP1/mTOR in clear cell ovarian cancer. Mol Endocrinol 24:447–463
93. Nan Y, Han L, Zhang A, Wang G, Jia Z, Yang Y, Yue X, Pu P, Zhong Y, Kang C (2010) MiRNA-451 plays a role as tumor suppressor in human glioma cells. Brain Res 1359:14–21
94. Nicholls PK, Harrison CA, Walton KL, McLachlan RI, O'Donnell L, Stanton PG (2011) Hormonal regulation of sertoli cell micro-RNAs at spermiation. Endocrinology 152:1670–1683
95. Noguchi S, Mori T, Hoshino Y, Maruo K, Yamada N, Kitade Y, Naoe T, Akao Y (2011) MicroRNA-143 functions as a tumor suppressor in human bladder cancer T24 cells. Cancer Lett 307:211–220
96. O'Donnell KA, Wentzel EA, Zeller KI, Dang CV, Mendell JT (2005) c-Myc-regulated microRNAs modulate E2F1 expression. Nature 435:839–843
97. Okamura K, Hagen JW, Duan H, Tyler DM, Lai EC (2007) The mirtron pathway generates microRNA-class regulatory RNAs in Drosophila. Cell 130:89–100
98. Olive V, Bennett MJ, Walker JC, Ma C, Jiang I, Cordon-Cardo C, Li QJ, Lowe SW, Hannon GJ, He L (2009) miR-19 is a key oncogenic component of mir-17-92. Gene Dev 23:2839–2849
99. Parker LH, Schmidt M, Jin SW, Gray AM, Beis D, Pham T, Frantz G, Palmieri S, Hillan K, Stainier DY et al (2004) The endothelial-cell-derived secreted factor Egfl7 regulates vascular tube formation. Nature 428:754–758
100. Perry MM, Williams AE, Tsitsiou E, Larner-Svensson HM, Lindsay MA (2009) Divergent intracellular pathways regulate interleukin-1beta-induced miR-146a and miR-146b expression and chemokine release in human alveolar epithelial cells. FEBS Lett 583:3349–3355
101. Pineau P, Volinia S, McJunkin K, Marchio A, Battiston C, Terris B, Mazzaferro V, Lowe SW, Croce CM, Dejean A (2010) miR-221 overexpression contributes to liver tumorigenesis. Proc Natl Acad Sci U S A 107:264–269

102. Qian P, Zuo Z, Wu Z, Meng X, Li G, Zhang W, Tan S, Pandey V, Yao Y, Wang P et al (2011) Pivotal role of reduced let-7 g expression in breast cancer invasion and metastasis. Cancer Res 71:6463–6474
103. Qin W, Dong P, Ma C, Mitchelson K, Deng T, Zhang L, Sun Y, Feng X, Ding Y, Lu X et al (2011) MicroRNA-133b is a key promoter of cervical carcinoma development through the activation of the ERK and AKT1 pathways. Oncogene doi:10.1038/onc.2011.561
104. Ren J, Zhu D, Liu M, Sun Y, Tian L (2010) Downregulation of miR-21 modulates Ras expression to promote apoptosis and suppress invasion of Laryngeal squamous cell carcinoma. Eur J Cancer 46:3409–3416
105. Roccaro AM, Sacco A, Thompson B, Leleu X, Azab AK, Azab F, Runnels J, Jia X, Ngo HT, Melhem MR et al (2009) MicroRNAs 15a and 16 regulate tumor proliferation in multiple myeloma. Blood 113:6669–6680
106. Rodriguez A, Griffiths-Jones S, Ashurst JL, Bradley A (2004) Identification of mammalian microRNA host genes and transcription units. Genome Res 14:1902–1910
107. Rogler CE, Levoci L, Ader T, Massimi A, Tchaikovskaya T, Norel R, Rogler LE (2009) MicroRNA-23b cluster microRNAs regulate transforming growth factor-beta/bone morphogenetic protein signaling and liver stem cell differentiation by targeting Smads. Hepatology 50:575–584
108. Roush S, Slack FJ (2008) The let-7 family of microRNAs. Trends Cell Biol 18:505–516
109. Ruby JG, Jan CH, Bartel DP (2007) Intronic microRNA precursors that bypass Drosha processing. Nature 448:83–86
110. Sahai E, Marshall CJ (2002) RHO-GTPases and cancer. Nat Rev Cancer 2:133–142
111. Saito Y, Liang G, Egger G, Friedman JM, Chuang JC, Coetzee GA, Jones PA (2006) Specific activation of microRNA-127 with downregulation of the proto-oncogene BCL6 by chromatin-modifying drugs in human cancer cells. Cancer Cell 9:435–443
112. Salvi A, Sabelli C, Moncini S, Venturin M, Arici B, Riva P, Portolani N, Giulini SM, De Petro G, Barlati S (2009) MicroRNA-23b mediates urokinase and c-met downmodulation and a decreased migration of human hepatocellular carcinoma cells. FEBS J 276:2966–2982
113. Sanchez-Carbayo M, Socci ND, Lozano J, Saint F, Cordon-Cardo C (2006) Defining molecular profiles of poor outcome in patients with invasive bladder cancer using oligonucleotide microarrays. J Clin Oncol 24:778–789
114. Sayed D, Abdellatif M (2010) AKT-ing via microRNA. Cell Cycle 9:3213–3217
115. Sayed D, He M, Hong C, Gao S, Rane S, Yang Z, Abdellatif M (2010) MicroRNA-21 is a downstream effector of AKT that mediates its antiapoptotic effects via suppression of Fas ligand. J Biol Chem 285:20281–20290
116. Schimanski CC, Frerichs K, Rahman F, Berger M, Lang H, Galle PR, Moehler M, Gockel I (2009) High miR-196a levels promote the oncogenic phenotype of colorectal cancer cells. World J Gastroenterol 15:2089–2096
117. Shi W, Gerster K, Alajez NM, Tsang J, Waldron L, Pintilie M, Hui AB, Sykes J, P'ng C, Miller N et al (2011) MicroRNA-301 mediates proliferation and invasion in human breast cancer. Cancer Res 71:2926–2937
118. Shin KH, Bae SD, Hong HS, Kim RH, Kang MK, Park NH (2011) miR-181a shows tumor suppressive effect against oral squamous cell carcinoma cells by downregulating K-ras. Biochem Biophys Res Commun 404:896–902
119. Smith AL, Iwanaga R, Drasin DJ, Micalizzi DS, Vartuli RL, Tan AC, and Ford HL (2012). The miR-106b-25 cluster targets Smad7, activates TGF-beta signaling, and induces EMT and tumor initiating cell characteristics downstream of Six1 in human breast cancer. Oncogene doi:10.1038/onc.2012.11
120. Soncin F, Mattot V, Lionneton F, Spruyt N, Lepretre F, Begue A, Stehelin D (2003) VE-statin, an endothelial repressor of smooth muscle cell migration. EMBO J 22:5700–5711
121. Taganov KD, Boldin MP, Chang KJ, Baltimore D (2006) NF-kappaB-dependent induction of microRNA miR-146, an inhibitor targeted to signaling proteins of innate immune responses. Proc Natl Acad Sci U S A 103:12481–12486

122. Ting Y, Medina DJ, Strair RK, Schaar DG (2010) Differentiation-associated miR-22 represses Max expression and inhibits cell cycle progression. Biochem Biophys Res Commun 394:606–611
123. Tsang WP, Kwok TT (2009) The miR-18a* microRNA functions as a potential tumor suppressor by targeting on K-Ras. Carcinogenesis 30:953–959
124. Tsukamoto Y, Nakada C, Noguchi T, Tanigawa M, Nguyen LT, Uchida T, Hijiya N, Matsuura K, Fujioka T, Seto M et al (2010) MicroRNA-375 is downregulated in gastric carcinomas and regulates cell survival by targeting PDK1 and 14–3-3zeta. Cancer Res 70:2339–2349
125. Uesugi A, Kozaki K, Tsuruta T, Furuta M, Morita K, Imoto I, Omura K, Inazawa J (2011) The tumor suppressive microRNA miR-218 targets the mTOR component Rictor and inhibits AKT phosphorylation in oral cancer. Cancer Res 71:5765–5778
126. Valadi H, Ekstrom K, Bossios A, Sjostrand M, Lee JJ, Lotvall JO (2007) Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. Nat Cell Biol 9:654–659
127. Valastyan S, Reinhardt F, Benaich N, Calogrias D, Szasz AM, Wang ZC, Brock JE, Richardson AL, Weinberg RA (2009) A pleiotropically acting microRNA, miR-31, inhibits breast cancer metastasis. Cell 137:1032–1046
128. Voortman J, Goto A, Mendiboure J, Sohn JJ, Schetter AJ, Saito M, Dunant A, Pham TC, Petrini I, Lee A et al (2010) MicroRNA expression and clinical outcomes in patients treated with adjuvant chemotherapy after complete resection of non-small cell lung carcinoma. Cancer Res 70:8288–8298
129. Wang B, Koh P, Winbanks C, Coughlan MT, McClelland A, Watson A, Jandeleit-Dahm K, Burns WC, Thomas MC, Cooper ME et al (2011) miR-200a Prevents renal fibrogenesis through repression of TGF-beta2 expression. Diabetes 60:280–287
130. Wang B, Majumder S, Nuovo G, Kutay H, Volinia S, Patel T, Schmittgen TD, Croce C, Ghoshal K, Jacob ST (2009) Role of microRNA-155 at early stages of hepatocarcinogenesis induced by choline-deficient and amino acid-defined diet in C57BL/6 mice. Hepatology 50:1152–1161
131. Wang C, Bian Z, Wei D, Zhang JG (2011) miR-29b regulates migration of human breast cancer cells. Mol Cell Biochem 352:197–207
132. Wang XF, Shi ZM, Wang XR, Cao L, Wang YY, Zhang JX, Yin Y, Luo H, Kang CS, Liu N et al (2011c) MiR-181d acts as a tumor suppressor in glioma by targeting K-ras and Bcl-2. J Cancer Res Clin Oncol 138(4):573–584
133. Wong QW, Ching AK, Chan AW, Choy KW, To KF, Lai PB, Wong N (2010) MiR-222 overexpression confers cell migratory advantages in hepatocellular carcinoma through enhancing AKT signaling. Clin Cancer Res 16:867–875
134. Xu B, Niu X, Zhang X, Tao J, Wu D, Wang Z, Li P, Zhang W, Wu H, Feng N et al (2011) miR-143 decreases prostate cancer cells proliferation and migration and enhances their sensitivity to docetaxel through suppression of KRAS. Mol Cell Biochem 350:207–213
135. Yanaihara N, Caplen N, Bowman E, Seike M, Kumamoto K, Yi M, Stephens RM, Okamoto A, Yokota J, Tanaka T et al (2006) Unique microRNA molecular profiles in lung cancer diagnosis and prognosis. Cancer Cell 9:189–198
136. Yang H, Kong W, He L, Zhao JJ, O'Donnell JD, Wang J, Wenham RM, Coppola D, Kruk PA, Nicosia SV et al (2008) MicroRNA expression profiling in human ovarian cancer: miR-214 induces cell survival and cisplatin resistance by targeting PTEN. Cancer Res 68:425–433
137. Yang JS, Lai EC (2011) Alternative miRNA biogenesis pathways and the interpretation of core miRNA pathway mutants. Mol Cell 43:892–903
138. Yang JS, Maurin T, Robine N, Rasmussen KD, Jeffrey KL, Chandwani R, Papapetrou EP, Sadelain M, O'Carroll D, Lai EC (2010) Conserved vertebrate mir-451 provides a platform for Dicer-independent, Ago2-mediated microRNA biogenesis. Proc Natl Acad Sci U S A 107:15163–15168

139. Yi R, Qin Y, Macara IG, Cullen BR (2003) Exportin-5 mediates the nuclear export of pre-microRNAs and short hairpin RNAs. Gene Dev 17:3011–3016
140. Yu J, Ryan DG, Getsios S, Oliveira-Fernandes M, Fatima A, Lavker RM (2008) MicroRNA-184 antagonizes microRNA-205 to maintain SHIP2 levels in epithelia. Proc Natl Acad Sci U S A 105:19300–19305
141. Zeng Y, Cullen BR (2003) Sequence requirements for micro RNA processing and function in human cells. RNA 9:112–123
142. Zeng Y, Cullen BR (2005) Efficient processing of primary microRNA hairpins by Drosha requires flanking nonstructured RNA sequences. J Biol Chem 280:27595–27603
143. Zhang H, Hao Y, Yang J, Zhou Y, Li J, Yin S, Sun C, Ma M, Huang Y, Xi J (2011) Genome-wide Functional Screening of miR-23b as a Pleiotropic Modulator Suppressing Cancer Metastasis. Nat Commun 2. doi:10.1038/ncomms1555
144. Zhang X, Liu S, Hu T, He Y, Sun S (2009) Up-regulated microRNA-143 transcribed by nuclear factor kappa B enhances hepatocarcinoma metastasis by repressing fibronectin expression. Hepatology 50:490–499
145. Zhang Y, Liu D, Chen X, Li J, Li L, Bian Z, Sun F, Lu J, Yin Y, Cai X et al (2010) Secreted monocytic miR-150 enhances targeted endothelial cell migration. Mol Cell 39:133–144
146. Zhao WG, Yu SN, Lu ZH, Ma YH, Gu YM, Chen J (2010) The miR-217 microRNA functions as a potential tumor suppressor in pancreatic ductal adenocarcinoma by targeting KRAS. Carcinogenesis 31:1726–1733