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Review

The involvement of microRNAs in malignant transformation

Zina Jeyapalan Rutnam[1,2] and Burton B. Yang[1,2]

[1]Sunnybrook Research Institute, Sunnybrook Health Sciences Centre, Toronto, Canada and
[2]Department of Laboratory Medicine and Pathobiology, University of Toronto, Canada

Summary. In the multiple steps in cancer progression, microRNAs (miRNAs) play significant roles in each stage. Reports of considerable differences in expression levels of miRNAs between normal and malignant tissues are understandable considering miRNAs are key regulators of gene expression. Dysregulation of miRNA expression levels in neoplasia occurs because many miRNAs are located in "fragile sites", which are frequently deleted in cancer. miRNAs are often down regulated in cancerous tissues and target oncogenic proteins are classified as tumour suppressor miRNAs, such as let-7. While, miRNAs that are frequently over-expression in neoplastic tissues compared to normal tissues and regulate tumour suppressor proteins are categorized as "oncomiRs". In this review, we summarize information about microRNAs involved in the emerging field of cancer stem cells, and microRNAs involved in breast cancer, an area of our expertise. The application of miRNAs to cancer therapeutics and diagnostics is emerging as an important field of gene therapy. The diverse nature of miRNAs in cancer is continually being elucidated to lead to the enigmatic treatment options for neoplastic disease.

Key words: Cancer stem cells, Breast cancer, Oncogenic miRNA, Cancer progression

Introduction

Cancer is a disease of unbalanced control of proteins that results in cell cycle deregulation and uncontrolled cell proliferation. Thus, it is not surprising that many studies have demonstrated that miRNAs are aberrantly expressed in cancer tissues. miRNAs are non-coding RNAs that are made up of 19-25 nucleotides and are able to modulate gene expression, primarily negativity by either blocking the translation or inducing degradation of target mRNA (Bartel, 2009). Malignant transformation is a multi-step process in which normal cells progress to cancer cells, in which they acquire a multitude of genetic and epigenetic alterations. These alterations were outlined by Hanahan and Weinberg in the "Hallmarks of Cancer: The next generation" (Olson et al., 2009). They recently updated the biological capabilities of cancer transformation to include deregulating cellular energetics, avoiding immune destruction, genome instability and mutation and tumor-promoting inflammation to the originally reported hallmarks: sustaining proliferative signalling, evading growth suppressors, enabling replicative immortality, activating invasion and metastasis, inducing angiogenesis and resisting cell death (Olson et al., 2009). In this review, we summarize the current understanding of the role of miRNAs in tumour progression and potential applications for their use in therapeutics and diagnostics.

Offprint requests to: B.B. Yang, Sunnybrook Research Institute, 2075 Bayview Avenue, Toronto M4N 3M5 Canada. e-mail: byang@sri.utoronto.ca

The involvement of microRNAs in cancer progression

miRNAs are non-coding RNAs that are made up of 18-25 nucleotides and are able to modulate gene expression, primarily negativity by either inducing the degradation or blocking translation of the target mRNAs (Bartel, 2009). miRNAs are highly conserved, which can be expressed in a tissue specific manner and perform essential functions in regulating diverse cellular processes (Dalmay and Edwards, 2006; Hua et al., 2006; Ruvkun, 2006; Foekens et al., 2008; Wang et al., 2008; Kahai et al., 2009; Lowery et al., 2009; Wickramasinghe et al., 2009; Yang et al., 2011; Luo et al., 2012). There are over 1000 miRNAs that have been sequenced and reported, and it is estimated that one third of genes are

regulated by miRNAs as one miRNA can regulate the expression of many genes (Lewis et al., 2005). miRNAs bind through imperfect base pairing to the 3'untranslated region (3'UTR) of target mRNAs (Ye et al., 2008). The binding specificity and efficiency is believed to be determined by 6-7 nucleotide sequence near 5? region of miRNA (Lewis et al., 2005). This sequence is called the "seed sequence" (Latronico et al., 2007), and is the initial binding site of the miRNA to the 3'UTR of the target mRNA (Lim et al., 2005). The degree of complementation of the seed sequence of miRNA to the target mRNA's 3'UTR also determines whether the mRNA is degraded or translational repression of protein production occurs (Berezikov et al., 2005; Lim et al., 2005). The mRNAs, which are targeted for degradation, are transported to p-bodies also leading to the translational repression of mRNAs (Liu et al., 2005). It is currently predicated that 10-30% of genes in higher eukaryotes can be regulated by miRNAs (Bartel, 2004). Adding to the complexity of miRNA function, recently miR-369-3 was shown to up-regulate tumour necrosis factor-α (Vasudevan et al., 2007). miR-369-3 directed the association of Argonaute (Ago) and fragile X mental retardation-related protein 1 with the AU-rich elements (AREs) in the 3'UTR to activate translation (Vasudevan et al., 2007). miR-378 and miR-93 can promote tumor growth and angiogenesis (Lee et al., 2007; Fang et al., 2011). Furthermore, miR-608 and miR-1293 have been shown to bind and repress human and viral interleukin-6 by directly binding to sites in their open reading frames in Kaposi's sarcoma-associated herpes virus infected cells (Kang et al., 2011). Deviations from the currently known miRNA processes function are still being elucidate and are frequently being updated.

microRNAs expression are frequently lost or amplified in a wide range of cancers. miRNA precursor processing has been shown to be reduced in cancer cells compared to normal human cell lines and tissues (Lee et al., 2008). These precursor miRNAs are not processed in mature miRNAs which results in a general decrease in miRNAs in neoplasias (Lu et al., 2005; Lee et al., 2008). In human cancers, TRBP mutations have been shown to cause defects in miRNA biogenesis, similar to the loss of PACT expression (Lee et al., 2006; Melo et al., 2009). Also, miRNA processing machineries, Drosha and Dicer, have a decreased expression in cancer cells. In ovarian cancer cases, the reduction of Dicer and Drosha correlates with a poor prognosis, suboptimal surgical cytoreduction and an advanced tumour stages (Merritt et al., 2008). Similarly, pleuropulmonary blastoma is caused by a nonsense mutation in the *DICER1* gene (Hill et al., 2009). However, microarray analysis has indicated that there is an increase in some miRNAs in tumour tissues. These miRNAs can be considered as oncogenes and their targets as tumour suppressors. For example, miRNAs miR-155 has an enhanced expression in breast, lung and colon tumours (Volinia et al., 2006). However, there are also under-expressed miRNAs, such as let-7, which have lower expression in lung tumours compared to in normal lung tissues (Johnson et al., 2005). These miRNAs act as tumour-suppressor genes and their modulation more likely reflects the loss of differentiation typical for tumour cells. Additionally, when putative targets of dysregulated miRNAs are tumour suppressors or oncogenes, the diseased process is amplified.

miR-124, one of many potential tumor suppressor miRNAs, plays a key role in neurogenesis (Cao et al., 2007). The miR-124 has 3 gene loci (miR-124-1, -2 and -3), which are frequently epigenetically silenced in breast, colon, lung, lymphoma and brain cancers (Lujambio et al., 2007; Hackanson et al., 2008; Silber et al., 2008; Agirre et al., 2009). These loci are also hypermethylated in the gastric mucosa of individuals infected with Helicobacter pylori and precancerous lesions (Ando et al., 2009). Consequently, it appears that silencing miR-124 is one of the aberrant genomic mutations that occur in the progression of many types of cancers. One of the targets of miR-124 is an oncogene CDK-6, involved in the phosphorylation of Rb. The epigenetic methylation of miR-124 results in increase levels of activated CDK-6, which in turn activates Rb to result in increased cell proliferation levels. However, the function of miR-124 is confounding and has not been fully understood yet because in acute lymphoblastic leukemia epigenetic silencing of miR-124 loci correlates with increased disease free survival (Roman-Gomez et al., 2009).

miR-203 is another potential tumor suppressor which is located in a fragile genomic site. It targets the 3'UTRs of ABL1 and BCR-ABL1, oncogenic fusion gene created by the Philadelphia translocation (Bueno et al., 2008). When miR-203 is silenced epigenetically, BCR-ABL1 fusion activation enhanced. This has been frequently observed in hematopoietic, oral, hepatocellular and various other types of carcinomas (Bueno et al., 2008; Kozaki et al., 2008; Furuta et al., 2010). Bmi-1, a member of a histone modifier complex that regulates gene expression, is also a target of miR-203. In experiments when miR-203 is ectopically expressed in cancer cells, there is a repression in cell growth and induction in apoptosis (Furuta et al., 2010).

When miRNAs negatively regulate gene expression of tumor suppressor genes, they are tumorigenic and considered "oncomiRs". One characteristic of "oncomiRs" is that they are up-regulated in cancers, such as miR-221 and -222 in aggressive CLL, thyroid carcinoma and hepatocellular carcinoma (Garofalo et al., 2012). Also, miR-221 is considerably over-expressed in triple-negative primary breast cancers (Radojicic et al., 2011). miR-221 and -222 are highly homologous miRNAs which impairs apoptosis and induces cell proliferation in different types of cancer cells (Rao et al., 2011; Garofalo et al., 2012). These functional changes occur because miR-221 and -222 are capable of targeting and down-regulating known tumor suppressors; p27, p57, PTEN and TIMP3 (Garofalo et al., 2012). In breast cancer cells, miR-221 and -222 results in the repression of TGF-ß-mediated growth inhibition and cells

becoming resistant to a selective estrogen receptor down-regulator drug, Fulvestrant (Rao et al., 2011).

miRNAs and cancer stem cells

Cancer stem cells (CSC) have the capability to differentiate into the different cell types found in a tumor and are responsible for instigating and sustaining tumor growth. CSCs divide by passing through a self-renewing mitosis; at least one daughter cell maintains the stem cell properties while the other can become a progenitor cell, which goes though regular mitotic cycles and differentiates (Shimono et al., 2009). This duplication system allows CSCs to proliferate and expand into highly malignant neoplasias (Shimono et al., 2009). Unfortunately, current cancer therapies, chemotherapy and radiation, are only able to decrease tumor size and cannot target CSCs and not result in long-term survival rates (Hatfield and Ruohola-Baker, 2008). CSCs are also resistant to multiple chemotherapy drugs because they have an increase expression of cell membrane efflux pump genes (Hatfield and Ruohola-Baker, 2008).

Studies have reported that miRNAs are able to control self-renewal and differentiation properties and thus are able to control CSC characteristics. miRNAs accomplish this by regulating the expression of target genes which are the key to maintaining CSC properties (Al-Hajj et al., 2004; Collins and Cheng, 2005; Xu et al., 2011). The miR-371-3 cluster behaves like stem cell promoting miRNAs and they are over-expressed in undifferentiated aggressive hepatoblastomas, while the miR-100/let-7a-2/miR-125b-1 cluster is down regulated (Cairo et al., 2010). In breast tumor-initiating cells, let-7 is decreased however its expression increases as the cells differentiate (Yu et al., 2007). Also, miR-205 and -22 are abundantly expressed in mammary progenitor cells, while miR-93 was at a low level. Another miRNA involved in inhibiting CSC characteristics is miR-34. It is a transcriptional target of p53 and is involved in inhibiting glioblastoma and prostate CSCs and controlling the biological characteristics of gastric and pancreatic CSCs (Godlewski et al., 2008; Ji et al., 2008, 2009; Liu et al., 2011). Restoration of miR-34 expression in these CSCs inhibits sphere formation *in vitro* and tumor regeneration *in vivo*, which are characteristics of stem-cells (Ji et al., 2009).

Breast cancer and miRNAs

Worldwide, breast cancer is the second most common type of cancer, after lung cancer. It has been reported that miRNAs are also aberrantly expressed in human breast cancer (Fig. 1). Most consistently miR-10b, miR-125b, miR-145, miR-21 and miR-155 have been shown to be deregulated in breast cancer (Iorio et al., 2005). miRNA expression can also be correlated with specific breast cancer biopathological features, such as estrogen and progesterone receptor expression, vascular invasion, lymph node metastasis, tumour stage and proliferation index.

Initially the role of miRNAs in metastasis was reported by Ma and colleagues who showed that breast cancer invasion and metastasis can be initiated by miR-10b (Ma et al., 2007). The function of miR-10b in breast carcinogenesis is interesting because it had no effect on proliferation by increased cell motility and invasion in SUM149 and HMECs, normally non-metastatic cell lines (Ma et al., 2007). Also, *in vivo* ectopic expression showed miR-10b increased the invasive behaviour and increased vascularisation of normally non-invasive breast cancer cells (Ma et al., 2007). Also compounding to the evidence of miR-10b involvement is its decreased expression in the majority of breast metastases compared to normal breast samples; the over-expression occurs in 50% of the samples (Ma et al., 2007). Twist, a transcription factor involved in the promotion of metastasis, was found to induce miR-10b expression (Ma et al., 2007). In addition, miR-10b targets HOXD10 which results in higher RhoC, a GTPase that promotes cytoskeleton remodelling, cell migration, tumour

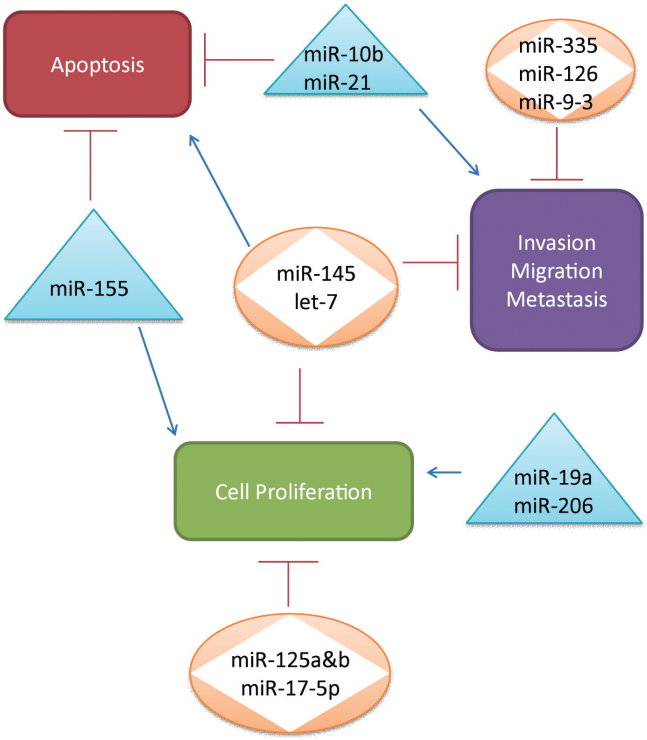

Fig. 1. Summary of miRNAs involved in breast cancer. miRNAs involved in apoptosis, cell proliferation and invasion, migration and metastasis of breast cancer cells. The blue triangles show miRNAs up-regulated in breast cancer progression and the orange circles are miRNAs that are down-regulated. Up-regulated miRNAs suppresses tumor suppressor gene expression, while down-regulated miRNAs suppress oncogene expression.

metastasis and invasion (McPherson et al., 2004; Ma et al., 2007). This is because HOXD10 is able to directly repress RhoC. These results are correlated with low HOXD10 expression in metastatic tumours.

miR-21 is also involved in the promotion of metastasis in cancers and is up regulated in many tumours (Chan et al., 2005). This is because it targets the 3'UTRs of PTEN, mapsin, tumour suppressor gene tropomyosin 1, and programmed cell death 4 (PDCD4) (Chan et al., 2005; Si et al., 2007; Zhu et al., 2007). Also, when antisense oligonucleotides against miR-21 were introduced into metastatic cancer cells, their metastatic ability was inhibited (Zhu et al., 2008).

On the other hand, Tavazoie and coworkers discovered metastasis suppressor miRNAs, miR-126, miR-206 and miR-335, which were decreased in metastatic nodules compared to non-metastatic breast cancer samples (Tavazoie et al., 2008). Furthermore, miR-126 and miR-335 were linked to metastatic-free survival (Tavazoie et al., 2008). The metastatic process is diminished because miR-335 negatively targets the SOX4 3'UTR; SOX4 is a transcription factor that promotes metastasis by the activation of tenascin C (Tavazoie et al., 2008). The knockdown by miR-335 of SOX4 transcription thus reduces the *in vitro* and *in vivo* metastatic and invasive potentials.

Other miRNAs involved in breast cancer include miR-145, which is also progressively down-regulated from normal breast tissue to cancer with high proliferation index (Spizzo et al., 2010). This is because miR-145 is able to activate the TP53 pathway by inducing p53 up-regulated modulator of apoptosis (PUMA) and P21, which is an inhibitor of cell cycle progression and decrease proliferation (Spizzo et al., 2010).

Furthermore, miR-145 suppresses invasion and metastasis by targeting metastasis gene, mucin 1 (Sachdeva and Mo, 2010). Similarly, miR-9-3 was down-regulated in breast cancers with either the presence of lymph node metastasis or high vascular invasion (Ma et al., 2010). This occurs because MYC, a transcription factor, binds to the miR-9-3 promoter and activates it. In turn, miR-9-3 down-regulates E-cadherin which causes the initiation of the ß-catenin pathway (Ma et al., 2010). This results in the increased expression the vascular endothelial growth factor gene which directs enhanced tumour angiogenesis (Ma et al., 2010). The expression of various let-7 miRNAs was also down-regulated in breast cancer tumours with characteristics of lymph node metastasis and higher proliferation index (Iorio et al., 2005).

Our understanding of the roles of miRNAs and other small ncRNAs play in cancer progression is still incomplete as there are many miRNAs and small ncRNAs that have been identified but still need to be classified and decipher their association in tumour progression. Many more investigations are required to profile the many small ncRNAs to understand their biological activities.

The use of ncRNAs in cancer therapeutics and diagnostics

Inherently, ncRNAs are involved in controlling the expression of multiple genes both at the transcriptional and post-transcriptional level through RNAi. Small ncRNAs that are naturally able to activate the RNAi pathway are siRNAs and miRNAs. Fundamentally, the therapeutic ability of individual ncRNA could be harnessed by regulating their expression level at the diseased site. Thus, the RNAi system is can be used in therapeutics to modulate the levels of miRNAs in diseases, especially cancer where their expression is widely altered. The expression of miRNAs can be increased in the case of tumor suppressor miRNAs, using the direct delivery of miRNA molecules, miRNA expression plasmids or other RNA- or DNA-based approaches (i.e. using miRNA molecules or miRNA expression vectors. One miRNA that can be used is let-7, as it is lost in many in many types of cancer (Calin et al., 2004). In lung cancer, let-7 greatly reduces growth in different lung cancer cell lines and xenografts of lung cancer mouse models (Esquela-Kerscher et al., 2008). In breast cancer, let-7 was drastically reduced in tumor-initiating cells compared to non-tumour-initiating cells and its expression level increased with differentiation (Yu et al., 2007). Furthermore, when let-7 was over-expressed into breast tumor initiating cells there was a reduction in proliferation, tumour formation, metastasis, and mammosphere formation (Yu et al., 2007). Also, the function of let-7 was shown when the antisense let-7 oligonucleotides increased the self renewal ability of non-tumour-initiating cells (Yu et al., 2007). It has also be shown to down-regulate several oncogenes, such as RAS, MYC and HMGA2 (Johnson et al., 2005; Mayr et al., 2007; Sampson et al., 2007). In order to target the let-7 molecules for lung cancer, intranasal administration has been tested in mice (Esquela-Kerscher et al., 2008). In K-ras mutant mice with lung cancer, an adenoviral vector with let-7 insert was intranasally inoculated along with Calcium phosphate precipitates which enhanced gene transfer in the lungs (Fasbender et al., 1998; Esquela-Kerscher et al., 2008). Using this method, let-7 and other small ncRNAs can also be used as a therapeutic to silence tumor promoting proteins. Individual miRNAs or siRNAs can be delivered to the diseased sites in order to down-regulate the level of anti-apoptotic or growth promoting proteins.

Oncogenic miRNAs can be controlled indirectly by regulating cellular factors that increases their expression. For example, oncogenic miRNA miR-155 expression is stimulated in breast cancer cells by inflammatory cytokines, interleukin-6 and IFN-γ (Jiang et al., 2010). If these molecules are suppressed, it would be possible to suppress the expression of miR-155 which is usually over-expressed in breast cancer cells. Unfortunately, at the present time the indirect regulation of miRNA expression has been unsuccessful due to the inability to control the specific of miRNAs that would be targeted.

Also, numerous studies have found the expression of oncogenic miRNAs can be reduced or silenced effectively and specifically by exogenously expressed non-coding oligonucleotides, both *in vitro* and *in vivo* (Hutvagner et al., 2004; Meister et al., 2004; Soutschek et al., 2004; Krutzfeldt et al., 2005). This method of intervention is a logical inhibitor because the base-pair interaction between the seed regions of miRNAs and mRNAs is essential for repressing mRNA function. These antisense molecules compete with mRNAs for miRNAs. Krutzfeldt and colleagues performed inhibition of four miRNAs by modified antisense RNAs, which they termed "antagomirs" *in vivo* (Krutzfeldt et al., 2005). Other types of oligonucleotides that have been used are locked nucleic acids, miRNA decoys and sponges (Krutzfeldt et al., 2005; Orom et al., 2006; Ebert et al., 2007; Haraguchi et al., 2009). These methods also often use viral vectors so the constructs can be expressed at high levels. For example, Gentner and colleagues used lentiviral vectors to over-express microRNA target sequences which lend to the specific knock down of microRNA miR-223 in mice (Gentner et al., 2009). The non-coding pseudogene PTENP1 has been shown to play roles in regulating tumor growth (Poliseno et al., 2010; Swami, 2010). The non-coding 3'UTR sequences of versican can modulate tissue development and tumor growth (Lee et al., 2009, 2010). Expression of he 3'UTR of CD44 regulates tumor growth and expression of matrix molecules (Jeyapalan et al., 2011; Jeyapalan and Yang, 2012), while expression of nephronectin 3'UTR promotes osteoblast differentiation (Lee et al. 2010).

One oncogenic miRNA that is currently being developed for therapeutics is miR-21. This miRNA is strongly and commonly up-regulated in many cancers, including lung, prostate, colon, breast, liver and stomach (Volinia et al., 2006; Meng et al., 2007; Zhu et al., 2007; Asangani et al., 2008; Fujita et al., 2008; Zhang et al., 2008b; Zhu et al., 2008; Bonci, 2010). It is classified as an "oncomiR" because it has been found to increase tumorigenicity by increasing cell cycle and invasion while inhibiting apoptosis (Krichevsky and Gabriely, 2009). Furthermore, miR-21 targets are well known tumor suppressors, PTEN, PDCD4, Tropomyosin 1, TIMP3 and NFIB, which are decreased in cancer tissues (Meng et al., 2007; Zhu et al., 2007; Asangani et al., 2008; Zhu et al., 2008). miR-21 is a potential therapeutic because miR-21 inhibitors increase apoptosis in hepatocellular carcinomas and glioma cells both *in vitro* and *in vivo* (Chan et al., 2005; Corsten et al., 2007; Connolly et al., 2008). In breast cancer, anti-miR-21 oligonucleotides were used as a treatment and found to successfully reduced breast cancer xenograft growth by 50% for 2 weeks (Si et al., 2007). Unfortunately, these oligonucleotides are inefficient for long term therapeutic use because of their unstable delivery to target sites. In extracellular fluids, the half-life of nucleic acids are limited to seconds due to nuclease enzyme degeneration in the body (Racz et al., 2011). Furthermore, they have a low cell membrane penetration due to the negative charge on nucleic acid molecules. However, this can be alleviated through the local injection of nucleic acids dissolved in great volumes aids in cellular uptake. This is because when injected at a high pressure, the pressure presses the nucleotides into the interstitial organs and across cell membrane into the cytoplasm, where they can be active. Also the large volumes decreases the efficiency of nucleases, thus more are delivered to the area of interest.

The potential of using miRNAs for cancer diagnosis, and prognosis is based on the observations from miRNA expression profiling studies which found differences in miRNA expression in normal and cancer tissues. Furthermore, in depth analysis with microarrays has found that tumour classification can be effectively performed as there are differences in miRNA expression between tumour types and grades (Lu et al., 2005). In colorectal cancer, the plasma levels of mir-29a and -92a correlates to advanced forms of the disease (Huang et al., 2010). While, a decreased expression of miR-143 and -145 were found in colonic carcinomas compared to normal tissues (Michael et al., 2003). Findings such have these have lead to the advent of tumour diagnostic chips that can be determine miRNA expression profiles (Zhang et al., 2008a; Wang et al., 2010). Furthermore, studies have shown that blood cells contain miRNA patterns that can be used to determine neoplasia (Hausler et al., 2010). Thus, miRNA signatures that correlated to diagnostic features of cancer can be used to establish treatment.

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