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Review

MicroRNAs and anticancer drugs

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MicroRNAs (miRNAs) are a class of small, non-coding, and endogenous RNA molecules, which are evolutionarily conserved but play a significant role in regulation of protein-coding gene expression at posttranscriptional and translational levels. Strikingly, a single miRNA is able to trigger hundreds of putative target genes by incomplete or complete complementary binding to their 3′ untranslated regions. Given their appearance in almost all types of tissues, miRNAs have been demonstrated to be intensively involved in normal and pathological processes of human cells. Aside from the role as invaluable biomarkers in indication of tumorigenesis and tumor progression, numerous studies have revealed the potential of miRNAs as novel targets of anticancer drugs in cancer therapy. In this review article, we focus on the summary of the latest publications on the topic of miRNA and anticancer drugs, and expect to shed light on understanding the molecular mechanisms of chemoresistance involving miRNA regulation. These pieces of evidence will eventually provide insight into the development of novel and more efficacious anticancer drugs in the future.

Keywords microRNA; cancer; chemoresistance; chemotherapy

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Introduction

MicroRNA (miRNA) is a class of small non-coding RNA molecules that mainly suppress gene expression at the post-transcriptional and translational levels by incomplete or complete complementary binding to target sequences within the 3′ untranslated regions (3′UTRs) [1]. Over the past decades, miRNA has become one of the hot topics in the field of cancer research, when studies have intensively demonstrated the important roles of miRNAs in normal cell differentiation and development, as well as in a variety of pathological processes, such as tumorigenesis [2].

The discovery of miRNAs was started by Lee and his colleagues in 1993 by then they found *lin-4*, a small RNA molecule that was capable of controlling the larval development of *Caenorhabditis elegans* [3]. Over the past 20 years, >2500 human miRNAs have been identified. The biogenesis of miRNA occurs in the nucleus and cytoplasm, which includes transcription, nuclear processing, nuclear export, cytoplasmic processing, and argonute assembly. It originates in the nucleus; miRNA gene is processed to double-stranded miRNA by RNA polymerase, transporter protein Exportin-5 and enzyme Dicer. Single-stranded mature miRNA is generated by helicase, and then combined with RNA-induced silencing complex (RISC), inhibits translation or induces mRNA cleavage [4,5]. Although the precise mechanisms of miRNA biological function have not been fully elucidated yet, it is found that each miRNA can regulate hundreds of target genes expressions simultaneously, while a single gene can also be targeted by multiple miRNAs. As such, the interaction between miRNAs and their cognate target genes enable miRNA be involved in various signaling pathways in the control of normal cell differentiation, division, and apoptosis [6,7]. Accordingly, the dysregulated miRNAs are assumed to cause tumorgenesis and tumor progression.

It has been reported that miRNA is able to control >30% of the protein-coding genes [8]. The mechanism of miRNA regulating gene expression involves the post-transcriptional and translational modulation based on two types of action: the first is the mismatched complementation between miRNA and target genes, which leads to the interference on normal translation process but not mRNA stability; the second is the perfect match between miRNA and target genes that induces the degradation of mRNAs [9]. Nucleotides 2–8 from the 5′ end of each mature miRNA sequence were demonstrated to play a significant role in binding to the target mRNAs, which is named seed sequence [10,11]. Given that the biological functions of miRNAs have been intensively studied, in this review article, we will focus on the latest progress in the research of miRNA and anticancer drugs.

MiRNA and Tumor

Numerous studies have documented the crucial roles of miRNAs in various types of human cancer. Certain miRNAs show obvious aberrance in tumors when compared with normal tissues. MiRNAs are often located in the fragile sites and the broken point areas, suggesting that they play an important role in tumor progression and metastasis [2,12,13]. Based on the various roles of their target genes in tumorigenesis, miRNAs can be named as oncogenic or tumor suppressor miRNAs. This means that miRNAs targeting oncogenes can be named as tumor suppressors, whereas oncogenic miRNAs are referred to as inhibitors of tumor suppressor genes. For example, Liu *et al*. reported that miR-27a could inhibit the growth of gastric cancer cells by targeting tumor suppressor, prohibitin (*PHB*) [14]. Decrease of miR-27a in gastric cancer cells can induce *PHB*, which suggests that miR-27a is an oncogenic miRNA. As a tumor suppressor, miR-145 was reported to repress the growth of ovarian cancer cells and angiogenesis through down-regulating hypoxia inducible factor 1 (*HIF1*) and vascular endothelial growth factor (*VEGF*). Given their signatures in tumor cells, miRNAs can serve as fine biomarkers for diagnosis and prognosis of different human cancers. For example, high expression of miR-20b and miR-150 or low expression of miR-451 is related to poor prognosis of cancer patients [15–17]. These findings suggest that ectopic expression of miRNAs in tumor may play dual roles as either oncogenes or tumor suppressors. Therefore, the study of miRNAs in tumors can help us understand the mechanism of gene regulation in the development of tumor. **Table 1** shows some well-studied oncogenes and tumor suppressor genes in human cancer, and the numbers of miRNAs that putatively target these genes are included as well. These data suggested that a single gene can be targeted by multiple miRNAs.

Let-7 is one of the most studied miRNAs in tumorigenesis. The human let-7 family consists of 13 members (let7-a-1, a-2, a-3, b, c, d, e, f-1, f-2 g, i, miR-98, and miR-202). It was reported that down-regulated let-7 in lung cancer is associated with increased *RAS* gene expression [18]. The further study confirmed that let-7 and 3′UTR of human *RAS* gene are complementary, resulting in inhibition of *RAS* gene expression. Moreover, let-7 was reported to negatively regulate other oncogenes and cell cycle regulators in various human cancers, such as *MYC, CDK6, Cyclin D, CCND2,* and *CDC25A*, leading to inhibition of cell proliferation by promoting the G1 to S phase transition [18–21]. In addition, let-7 can target the expression of high-mobility group AT-hook 2 (*HMGA2*), which is an oncogene with a high mutation rate in many types of cancer cells [20]. There are 7 binding sites between let-7 and 3′UTR of *HMGA2* mRNA, and the destruction of these binding sites could reduce the let-7 mediated down-regulation of *HMGA2*, resulting in the growth of non-adherent cancer cells [20,22]. Recent studies showed that let-7 can also regulates metastasis-related genes, such as myosin heavy chain 9 non-muscle (*MYH9*) and C-C chemokine receptor type 7 (*CCR7*) [23,24]. **Figure 1** illustrates the key tumor suppressor roles of let-7.

Microarray expression profiling analyses have revealed a global reduction of miRNA expression in various cancer models [25]. This observation led to the hypothesis that the mediators involved in the molecular machinery of miRNA maturation, such as Dicer, could be dysregulated in tumor tissues. The failure to properly express or process miRNAs

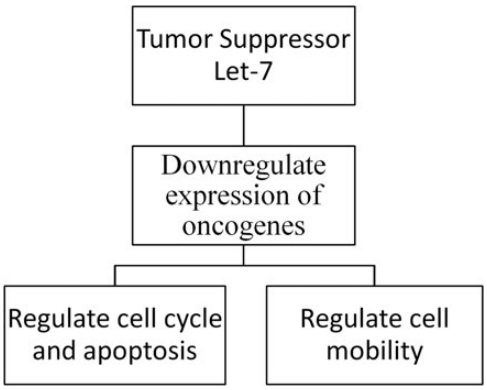

Figure 1. Tumor suppressor role of let-7

Table 1. Selected oncogenes and tumor suppressor genes in human cancer

Oncogene	Ensembl Gene ID	Number of miRNAs[a]	Tumor suppressor	Ensembl Gene ID	Number of miRNAs[a]
ABL1	ENSG00000097007	52	*BRCA1*	ENSG00000012048	253
BRAF	ENSG00000157764	155	*CDKN1A*	ENSG00000124762	101
CTNNB1	ENSG00000168036	148	*CDKN2A*	ENSG00000147889	9
FOS	ENSG00000170345	84	*PTEN*	ENSG00000171862	489
KRAS	ENSG00000133703	249	*RB1*	ENSG00000139687	170
MDM2	ENSG00000135679	205	*TP53*	ENSG00000141510	50
MYC	ENSG00000136997	34	*WT1*	ENSG00000184937	121

[a]The numbers of miRNAs that target the selected oncogenes and tumor suppressor genes were analyzed by using the web interface microT-CDS at the DIANA-LAB (http://diana.imis.athena-innovation.gr/DianaTools/index.php?r=microT_CDS/index).

resulting from the decreased Dicer expression is associated with various aspects of malignant progression [26]. Dicer is an RNase III enzyme essential for the maturation of the majority of miRNAs [27]. It plays an important role in the cleavage of pre-miRNAs into their mature forms and has previously been implicated in the oncogenic process of several cancers [28]. Previous studies have suggested that a reduction in the expression of certain miRNAs, or an overall decrease in miRNAs processing through partial depletion of Dicer, could promote the potential of tumor metastasis [26]. Lower expression of Dicer was also found to be associated with advanced tumor stages and poor clinical outcome in melanoma [29], breast cancer [30], lung cancer [31], and ovarian cancer [32].

Recent studies have shown that the single nucleotide polymorphisms (SNPs) contained in the interaction regions between the miRNA seed sequences and the target gene 3′-UTRs are associated with the occurrence and development of tumor. As potential biomarkers, these SNPs are of attention [33,34]. Through the database analysis, researchers found that SNPs in miRNAs occur less frequently than in other loci in genome, which may be because of the high conservation of miRNAs sequences. Mishra *et al*. reported that 3′-UTR polymorphism C-T of dihydrofolate reductase (*DHFR*), a target gene of miR-224, decreased the binding between miR-224 and *DHFR*, thus elevating the translation of *DHFR* mRNA, eventually resulting in reduced sensitivity to methotrexate in human fibrosarcoma HT1080 cells [35]. They also found that a SNP in the precursor could influence the expression of miR-2146a, thereby affecting the expression of its target genes, *BRCA1* and *BRCA2* [35]. In support these results, Shen *et al.* reported that this SNP correlated to the onset age of familial breast and ovarian cancer [36]; and their newer results showed that the C/T SNP in miR-217 affected the formation of the secondary structure, resulting in alteration in the expression of *BRCA1* [37].

MiRNAs and Anticancer Drugs

Given the importance of miRNA in human cancer, it is meaningful to study the alteration of miRNA in response to chemo drug treatments, which may provide a novel insight into the understanding the molecular basis of chemotherapy and help develop safer and more efficacious drugs to treat human cancers. Numerous studies have documented the miRNA profiles in response to various chemotherapies by using different experimental models and discovery strategies. Here, we will discuss a couple of example studies.

Xie *et al*. examined the expression profile of miRNAs and their target genes in human chronic myelogenous leukemia K562 cells, and they found that miR-16, miR-34a-c, miR-17-5p, and miR-125 were up-regulated, while miR-106 and miR-150 were down-regulated in response to the treatment with cisplatin [38]. MiR-16, miR-34a-c, and miR-17-5p were proved to regulate the expression of *Bcl2, E2F1*, and *E2F3*, respectively; and *RB1* and *p53* were targeted by miR-106 and miR-150. It was demonstrated that cisplatin-induced apoptosis in K562 cells either by reducing miR-106 that up-regulated *RB1* or by inhibiting miR-150 that increased *p53* expression. The interaction between miRNAs and their target genes is illustrated in **Table 2**. After treated breast cancer MCF-7 cells with 5-fluorouracil (5-FU), Shah *et al.* studied miRNA expression and found that 42 miRNAs were differentially expressed. Of which, 23 miRNAs were up-regulated and 19 miRNAs were down-regulated [39]. Target prediction and gene ontology analysis suggested that potential target genes of these differentially expressed miRNAs were oncogenes or tumor suppressor genes related to programmed cell death, activation of immune response, and cellular catabolic processes. Zhou *et al.* found that 56 up-regulated and 50 down-regulated miRNAs were identified in colon cancer cells treated with 5-FU or oxaliplatin when compared with the non-treated control cells. The down-regulations of miR-197, miR-191, miR-92a, miR-93, miR-222, and miR-1826 were further validated [40].

MiRNAs and the Resistance of Anticancer Drugs

The resistance of chemotherapy is still one of the major challenges towards the current anticancer treatment in clinic and plays a key role in death from cancer. As such, it is of importance to understand the molecular basis of chemoresistance. More and more evidence showed that aberrant expression of miRNAs is significantly correlated with the anticancer drug resistance, and the mechanism of action may attribute to the master regulatory role of miRNAs in expression of their cognate target genes [2,41–43]. Chemotherapy is still one of the most used strategies to treat cancer; however, owing to the primary or acquired drug resistance, anticancer drugs cannot kill the tumor cells, leading to tumor relapse. Recent studies showed that certain miRNAs changed were altered in the drug-resistant cancer cells. For example, decreased miR-200b, miR-194, and miR-212 and increased miR-192, miR-424, and miR-98 were found in docetaxel resistant non-small cell lung cancer, indicating the potential role of miRNAs in chemoresistance [44].

Table 2. Interaction between miRNAs and their target genes responding to cisplatin in K562 cells

MiRNAs	Target genes
Up: miR-16, miR-34, miR-17-5p, miR-125 Down: miR-106, miR-150	Down: *Bcl2*, *E2F1*, *E2F2*, Up: *RB1*, *P53*

Owing to the complexity of drug resistance, a clear understanding of the molecular basis is still lacking. Some studies reported that chemoresistance might involve a variety of factors including individual variations in patients and genetic/epigenetic differences in tumors, such as alterations in drug transport system leading to the decrease of the intracellular concentration of the drug and increase of drug efflux from cancer cells; tumor emerging metabolism resistance through altering the activation or detoxification of drugs; and increased repair of DNA damage and decreased sensitivity due to induction of apoptosis [45–48]. Although the complete understanding of drug resistance has not been achieved to date, a number of studies have concluded that the following mechanisms involving miRNAs may play significant roles in this action.

First, chemoresistance is associated with apoptosis mediated by miRNA. For example, anti-apoptotic protein Bcl-2 is highly expressed in many tumors and accounts for multidrug resistance. A number of studies have demonstrated miR-21, miR-15b/16, miR-34a, miR-181b, and miR-497 can repress Bcl-2 and improve drug sensitivity [49–51]. Second, chemoresistance is associated with drug transport mediated by miRNA. Pan *et al*. have reported that miR-328 can down-regulate breast cancer resistance protein ABCG2. In drug-resistant breast tumor MCF-7/MX100 cells, over-expression of miR-328 can reverse the suppression on ABCG2, thereby increasing tumor cell sensitivity to mitoxantrone [52]. Kovalchuk *et al*. found that in multi-drug resistant breast tumor MCF-7/DOX cells, over-expressed miR-451 could reduce the level of multidrug resistance protein 1 (*MDR1*) expression, resulting in the increase of cell sensitivity to doxorubicin [53]. Third, chemoresistance is associated with cellular repair mediated by miRNA. Recent studies reported that miR-182 mediated *BRCA-1* down-expression, so as to impede DNA repair, thus affecting the effectiveness of chemotherapy in breast cancer. *BRCA-1* belongs to the tumor suppressor gene and is associated with DNA double-strand break repair system; high expression of *BRCA-1* indicates poor efficacy of platinum drugs or resistance [54,55]. Forth, chemoresistance is associated with endocrine therapy mediated by miRNA. The efficacy of endocrine therapy in breast cancer and prostate cancer has been confirmed. In breast cancer, tamoxifen is widely used in the estrogen receptor (ER)-positive patients. However, breast cancer cells with higher levels of miR-221/222 expression are more resistant to tamoxifen. One of the possible mechanisms is that miR-221/222 can inhibit the expression of *p27* gene [56], and their inhibitory effect on ER expression was also reported to be responsible, at least in partial, for the resistance of tamoxifen [57].

Some other studies provided additional insights into drug resistance. For example, 17 miRNAs were found abnormally expressed in multi-drug resistant breast cancer MCF-7/VP cells and tumor tissues [58]. MiR-187, miR-326, miR-429, and miR-7 were significantly down-regulated. Restoring the expression of miR-326 decreased the expression of multidrug resistance-associated protein 1 (MRP1/ABCCl) and increased the sensitivity of tumor cells to etoposide and doxorubicin. The study is the first one to show that miRNA can adjust multidrug resistance through MRP1, suggesting that miR-326 may be an important target for preventing and reversing multidrug resistance in tumor cells [58]. Expressions of miR-497 and miR-181b were decreased in the multidrug resistant gastric cancer SGC7901/VCR cells. Further study showed that the co-target of miR-497 and miR-181b was *Bcl-2* gene and restoring the expression of miR-181b improved resistant gastric cancer SGC7901/VCR and lung cancer A549/cisplatin cells sensitivity to chemo drugs such as vincristine, 5-FU, cisplatin, etoposide, and adriamycin [59,60]. Compared with the parent gastric cancer SGC7901 cells, 10 miRNAs were significantly down-regulated in multidrug-resistant SGC7901/VCR cells. Over expression of miR-15b and miR-16 enhanced the sensitivity to vincristine, adriamycin, etoposide, and cisplatin through down-regulation of Bcl2 [61].

Potentials of MiRNA in Clinic Application

MiRNA is a set of regulatory molecules in the process of gene expression and protein translation; they play a pivotal role in the development of cancer. Given the superior roles of miRNAs in regulating their target gene expression, studies have shown that dysregulation of certain miRNAs are involved in control of proliferation and invasion of cancer cells. MiRNA binding to specific target mRNA, negatively regulate the transcription and translation of the target mRNA transcripts. Owing to their unique signatures, miRNAs have a natural likelihood as targets in cancer gene therapy. A single miRNA can trigger hundreds of putative targets, whereas one gene can be regulated by multiple miRNAs at the same time. Therefore, because of ectopic expression of certain miRNAs in a variety of solid tumors and hematological malignancies, alternation of miRNA expression in the target tissues has a potential to lead to novel gene therapy in the future.

Exogenous miRNAs can be delivered into cells by the specific carrier and recover the loss of tumor suppressor miRNAs in target tissues. For example, Takamizawa *et al*. reported that transfecting let-7 into lung adenocarcinoma cell line A549 can reduce cell colony formation [62]. Xu *et al*. reported that miR-145 can inhibit the expression of *p70S6K1* leading to the suppression of the growth of ovarian cancer cells and angiogenesis [17]. Given *RAS* gene being targeted by both miR-143 and miR-145, in pancreatic cancer cells with *KRAS* mutation, the induction of miR-143 and miR-145 can significantly inhibit tumor formation [63].

Oncogene *ERBB2/3* is reported to promote tumor cell growth and invasion. Scott *et al*. transfected miR-125a/b into human breast cancer SKBR3 cells by retroviral vectors, and successfully inhibited the transcription and translation of *ERBB2/3* [64]. Compared with normal breast tissue, miR-205 was significantly reduced in breast tumor tissues. Over-expression of miR-205 can promote apoptosis in breast cancer SKBR3 cells by targeting and repressing *HER3* and protein kinase B *(PKB*) [65].

It was found that certain miRNAs were significantly induced in cancer cells, suggesting that these small molecules may promote tumor to occur and develop. As such, these oncogenic miRNA can be down-regulated to achieve a therapeutic effect. MiR-21 is one of the most studied oncogeneic miRNAs, and it is highly expressed in nearly all solid tumors. Si *et al*. transfected MCF-7 cells with the 2-*O*-methyl oligonucleotide complementary to miR-21 versus the negative control oligonucleotides, the cells were then injected into the mammary pads of female nude mice. Their results showed that the anti-miR-21 group developed smaller tumors (up to 50%) when compared with the control group [66]. It was also reported that miR-483-3p could inhibit the expression of platelet-derived growth factor subunit B (*PDGFB*), leading to reduction of the human umbilical vein endothelial cell proliferation, migration, and blood vessel formation. In addition, miR-483-3p could inhibit Akt protein phosphorylation in the PI3K-Akt signaling pathway due to negative regulation on *PDGFB*, leading to the repression of tumor cell invasion and metastasis in the referred models [67].

Jiang *et al*. evaluated expression of certain miRNAs in 28 patients treated with S-1/oxaliplatin and 27 patients with doxifluridine/oxaliplatin, and concluded that miRNAs could be used as valuable prognostic markers. They computed the correlation between the expression levels of miRNAs (let-7g, miR-200c, miR-21, miR-140, miR-192, and miR-181b) and prognosis of gastric cancer patients in stages III and IV. The results showed that the expressions of miR-181b ($P = 0.0028$) and miR-21 ($P = 0.0001$) were significantly higher in cancer tissue than in normal tissue. Kaplan–Meier survival analysis showed that low expressions of miR-21 ($P = 0.0004$) and miR-181b ($P = 0.018$) were closely correlated to the overall survival in patients treated with S-1 and doxifluridine-based therapies, suggesting that miR-21 and miR-181b are useful biomarkers for prognosis of advanced gastric cancer [1,68,69]. In support of these results, miR-215 was demonstrated to correlate with the prognosis of a group of stages II and III colon cancer patients [1].

At present, miRNAs in cancer stem cells (CSCs) attracted significant attention when studying chemoresistance. The CSCs theory suggests that there is a small portion of cells in tumor tissue having characteristics of unlimited proliferation, self-renewal, high tolerance to chemotherapy, high tumorigenic ability, and these cells are involved in chemoresistance and tumor recurrence. Many miRNAs have been reported to be dysregulated in a variety of CSCs and influence the expression of the cognate target genes to regulate the malignant behavior of CSCs. Yu *et al.* found a large number of $CD44^+/CD24^-$ stem cells in breast cancer tissue, but the expression of let-7 was significantly reduced in these CSCs [70]. They further found that forced expression of let-7 by letiviral vectors can inhibit breast CSCs proliferation, tumor formation, tumor sphere formation, and metastasis in both *in vitro* and *in vivo* [70]. Their subsequent study also found the low expression of miR-30 in breast $CD44^+/CD24^-$ CSCs or serum-free culture tumor cells sphere. MiR-30 was able to regulate stem cell self-renewal and apoptosis through the inhibition of ubiquitin-conjugating-9 (*Ubc9*) and integrin β3 *ITGB3*) [71]. High expression of miR-30 can inhibit tumor formation in NOD/SCID mice by breast CSCs and the metastasis to lung [71]. Cheng *et al.* found that in ovarian malignancies, $CD44^+/CD117^+$ cells had higher proliferation rate versus relatively low differentiation along with the resistance to conventional chemotherapy. MiR-199a can negatively regulate CD44 expression in these ovarian CSCs [72]. Transfection of miR-199a can cause reduction of CD44 expression, arrest of G2/M phase, and down-regulation of the multidrug resistance gene ATP-binding transporter protein G superfamily member 2 (*ABCG2*), which is potentially responsible for the inhibition of tumor cell proliferation, tumor formation, metastasis, and tumor sensitization to cisplatin, paclitaxel, and doxorubicin *in vivo* [72].

Even with a great potential to become a novel therapeutic strategy for cancer treatment, it is still too early to translate miRNA target therapy into clinical application, given the non-specific targeting signature of miRNA that is associated with the unpredictable toxicities. More basic and translational researches are needed to be done for better understanding the regulatory basis of miRNA in gene expression and overcome the natural non-specific targeting weaknesses of this class of small molecules for cancer therapy.

Conclusions and Prospective

MiRNAs have been documented to be involved in tumorgenesis and progression. Strong evidence supports that miRNAs are eligible for acting as promising biomarkers in cancer diagnosis, prognosis, chemotherapeutic response, and novel targets for treatment as well. In addition, miRNAs have showed unique advantages due to their stability. For example, miRNAs can be detected from paraffin-embedded tumor tissue, serum, pleural effusion, and sputum.

Further study of the mechanism of miRNAs will provide more new drug targets for cancer therapy. Drugs for regulating miRNA expression are expected to be widely used in the

targeted therapy of cancers; however, there are many questions needed to be addressed. First, the function of majority of miRNAs is unclear. At present, the loss or gain of function strategy is mainly used to investigate the function of miRNAs. More studies are needed to clarify the role of miRNAs in cancer. Second, the targets of miRNAs need to be identified. Each miRNA can regulate hundreds of target genes according to bioinformatic prediction; therefore, to functionally validate the global targets of the miRNAs remains a challenge in miRNA research. Third, the mechanism by which chemo drugs regulate miRNAs expression needs to be better elucidated. Nevertheless, we believe that, with more and more valid experimental and clinical evidence, miRNAs will be recognized as crucial biomarkers for different types of human tumor and critical players in the future cancer therapeutics.

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