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REVIEW

MicroRNAs and drug modulation in cancer: an intertwined new story

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Abstract **MicroRNAs (miRNAs) are endogenous small non-coding RNAs (ncRNAs) which play important regulatory roles in physiological processes such as cellular differentiation, proliferation, development, apoptosis and stem cell self-renewal. An increasing number of papers have clearly claimed their involvement in cancer, providing, in some cases, also the molecular mechanisms implicated. Several studies led to the conclusion that miRNAs can be effectively used as anticancer agents alone or in combination with existing anticancer drugs. In particular, miRNAs can be effectively used to overcome drug resistance, one of the main factors responsible for anticancer treatment insuccess. One of the main questions remains how to modulate the expression of miRNAs in cancer cells. Interestingly, a few studies have shown that the expression of miRNAs is affected by drugs (including some drugs currently used as anticancer agents), therefore providing the rationale for an intertwined scenario in which miRNAs can be modulated by drugs and, in turn, can affect drug sensitivity of cancer cells.**

Keywords miRNAs, cancer, multidrug resistance, transcription factor, chemotherapy

Introduction

MicroRNAs (miRNAs) are 18 to 24 nucleotide noncoding RNAs (ncRNAs) whose role in human carcinogenesis has been relatively recently identified. They exert regulatory functions of gene expression by controlling the translation and the degradation of their mRNA targets and they are involved in a variety of biological processes (Ambros and Lee, 2004; Bartel, 2004; He and Hannon, 2004; Pasquinelli et al., 2005; Plasterk, 2006; Carleton et al., 2007). First transcribed in the nucleus by RNA polymerase II/III as long, capped and polyadenylated precursor (pri-miRNA) (Cai et al., 2004; Lee et al., 2004; Borchert et al., 2006) miRNA is then processed into a 70 to 100 nucleotide hairpin-shaped RNA (pre-miRNA) by a double-stranded RNA-specific ribonuclease called Drosha, in conjunction with its binding partner DGCR8 (DiGeorge syndrome critical region gene 8, or Pasha) (Cullen, 2004). By means of Exportin 5, pre-miRNA is translocated to the cytoplasm, where a ribonucleic complex, composed of Dicer (a ribonuclease III) and TRBP (HIV-1 transactivating response RNA binding protein) cleaves it into a 18–24 nucleotide duplex that interacts with a large protein complex called RISC (RNA-induced silencing complex), which includes proteins of the Argonaute family (Ago1–4 in humans). One strand of the miRNA duplex remains stably associated with RISC and guides it mainly, but not exclusively, to the 3′-untranslated region (3′-UTR) of the target mRNAs. Several experiments using artificial sites show that targeting can also occur in the 5′-untranslated region (5′-UTR) and ORFs (open reading frames): endogenous ORF targeting appears to be less frequent and less effective than 3′-UTR targeting but much more frequent than 5′-UTR targeting (Lytle et al., 2007; Qin et al., 2010). The target mRNA can subsequently either undergo cleavage in the case of a miRNA:mRNA perfect base pair complementarity (occurring mainly in plants) or translational silencing of the target in the case of an imperfect complementarity (predominant in nematodes and mammals), although also in case of imperfect base pairing a reduction of the target mRNA has been described (He and Hannon, 2004). Recently, it was discovered that some miRNAs are also able

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to upregulate translation of their specific mRNA target. In fact, in a cell cycle arrest state, it seems that miRNAs can activate the expression of a target gene by recognizing target sites in the AU-rich elements (ARES) present in the 3′-UTR regions of the messenger with the help of proteins such as AGO and FXR1 (Vasudevan et al., 2007). It is easy to understand the extensive miRNAs involvement in cancer. Some miRNAs might have a dual nature in cancer cells. Onco-miRNAs and suppressor-miRNA may represent two different sides of the same gene, acting in one way or another depending on the type of tissue and specific target (Fabbri et al., 2007). The study of miRNome (defined as the full complement of miRNA expression in a given genome) has shown that several drugs can directly or indirectly (e.g. by modulating the expression of transcription factors) modulate the expression of miRNAs. On the other hand, miRNAs can target genes responsible for drug-resistance/sensitivity. Therefore the understanding of the interaction mechanisms between miRNA and drugs could be critical for future applications in the pharmaceutical field. This review will focus on the role of miRNAs both as regulators of drug sensitivity and as targets for drugs that regulate their expression.

miRNAs as drug sensitivity/resistance modulators

miRNAs involved in multidrug resistance (MDR) are summerized in Table 1.

In cancer patients, MDR is the major clinical obstacle to the success of chemotherapy and leads to poor prognosis (Szakács et al., 2006). MDR is considered as a multifactorial phenomenon whose key determinants remain unfortunately largely unknown. The evidence of the roles of miRNAs in determing drug sensitivity/resistance has been emerging and extensive studies have indicated that the acquisition of MDR by tumor cells can be modulated by changes in miRNA levels, too. In fact, more and more reports confirmed an involvement of miRNAs in the mechanism of chemoresistance (Zheng et al., 2010) and the modulation of these molecules may indeed allow an increased sensitivity of tumor cells to chemotherapeutic agents.

The first evidence to indicate a possible link between miRNA dysregulation and cancer drug resistance was provided in a recent study by Climent et al. (2007) who suggested that the increased sensitivity of breast cancer patients to anthracycline-based chemotherapy may be related to the deletion of chromosome 11q, a region containing the *miR-125b* gene.

Regarding the role of miRNAs in the resistance of human MCF-7 breast adenocarcinoma cells to doxorubicin (DOX), Kovalchuk et al. (2008) showed first that DOX-resistant MCF-7 cells exhibited a substantial deregulation of the miRNome profile and altered expression of miRNA processing enzymes Dicer and Argonaute 2. Moreover, they demonstrated that microRNA-451 (*miR-451*) regulates the expression of the multidrug resistance 1 (*mdr1*) gene, a crucial factor in drug resistance. Transfection of the MCF-7/DOX-resistant cells with *microRNA-451* resulted in the increased sensitivity of cells to DOX, suggesting that adjustment of miRNA altered expression may have significant implications for therapeutic strategies aiming to overcome cancer cell resistance. Similarly, another group explored the role of miRNAs in acquiring resistance to tamoxifen, a drug successfully used to treat women with estrogen receptor-positive breast cancer. By miRNA microarray analysis of MCF-7 cell lines they found a significantly increased expression of 8 and downregulation of 7 miRNAs in a tamoxifen-resistant breast cancer cell line compared with parental tamoxifen-sensitive cells. In addition, they revealed that the expression of *miR-221* and *miR-222* was also significantly higher in HER2/neu-positive primary human breast cancer tissues that are known to be resistant to endocrine therapy compared with HER2/neu-negative tissue samples. By directly targeting p27(Kip1), *miR-221*/*222* increase tamoxifen resistance; this observation confirms a relationship between *miR-221/222* expression and HER2/neu overexpression in primary breast tumors that are generally resistant to tamoxifen therapy (Miller et al., 2008). By comparing global miRNA and mRNA expression patterns, Xin et al. (2009) examined the role of miRNAs in resistance to the "pure antiestrogen" fulvestrant, using fulvestrant-resistant MCF7-FR cells and their drug-sensitive parental estrogen receptor (ER)-positive MCF7 cells. They identified 14 miRNAs downregulated in MCF7-FR cells and found a negative correlation between expression of these miRNAs and their predicted target mRNA transcripts. An even stronger negative correlation was also found in genes regulated by multiple miRNAs or having multiple miRNA-targeting sites. Pathway analyses predicted these miRNAs to regulate specific cancer-associated signal cascades.

All these results suggest a significant role for miRNA-regulated gene expression in the onset of breast cancer drugs resistance and an improved understanding of this trend could lead to better therapies for this type of tumor.

In gastric cancer, the mechanisms responsible for MDR have been widely explored, but they have not been completely characterized yet. In a recent study, miRNA expression profiling showed a restricted set of de-regulated miRNAs in MD-resistant gastric cancer cell line SGC7901/VCR compared to its parental SGC7901 cell line. SGC7901/VCR cells frequently have deletions within the 7q22 region where the gene encoding for *miR-106b* lies (7q22.1). Among the downregulated miRNAs, there are *miR-15b* and *miR-16*, whose expression was inversely correlated to that of Bcl2 protein in SGC7901/VCR cells. This finding suggested that *miR-15b* and *miR-16* could play a role in the modulation of the susceptibility of gastric cancer cells to chemotherapeutic drug-induced apoptosis by directly targeting BCL2 (Xia et al.,

Table 1 miRNAs involved in multidrug resistance

miRNA	Up/downregulation	Correlation with sensitivity to chemotherapy	Chemotherapeutic agent	Tuomor type	Author
miR-125b	↓	↑	Anthracycline	Breast	Climent et al., 2007
miR-451	↓	↓	Doxorubicin	Breast	Kovalchuk et al., 2008
miR-221 *miR-222*	↑	↓	Endocrine therapy Tamoxifen	Breast	Miller et al., 2008
miR-let7i *miR-181a* *miR-191* *miR199bi* *miR-204* *miR-211* *miR-212* *miR-216* *miR-328* *miR-346* *miR-373** *miR-424* *miR-628* *miR-768-3p*	↓	↓	Fulvestrant	Breast	Xin et al., 2009
miR-15b *miR-16*	↓	↓	Vincristine adriamycin 5-fluoruracil cisplatin mitomycin C etoposide	Gastric	Xia et al., 2008
miR-30c *miR-130a* *miR-335*	↓	↓	Paclitaxel cisplatin	Ovarian	Sorrentino et al., 2008
miR-214 *miR-199a** *miR-200a* *miR-100* *miR-125b* *let-7 cluster*	↓	↓	Cisplatin	Ovarian	Yang et al., 2008
miR-221 *miR-222*	↑	↓	Tumor necrosis factor-related apoptosis-inducing ligand	NSCLC	Garofalo et al., 2008
miR-34a	↓	↓	Camptotechin	Prostate	Fujita et al., 2008

2008).

Sorrentino et al. (2008), after analyzing miRNAs profile in paclitaxel- and cisplatin-resistant ovarian cancer cell lines, observed that drug resistance is associated with a distinct miRNA fingerprint including a panel of 6 miRNAs (*let-7e*, *miR-30c*, *miR-125b*, *miR-130a*, *miR-335*) which were always differentially expressed in all the resistant cells. Among them, *miR-30c*, *miR-130a* and *miR-335* appeared downregulated in all the resistant cell lines, suggesting their involvement in the development of chemoresistance. Interestingly, *miR-130a* downregulation was linked to the translational activation of the M-CSF gene, a known resistance factor for ovarian cancer. Yang et al. (2008) also showed that several miRNAs are altered in human ovarian cancer, with the most significantly deregulated miRNAs being *miR-214*, *miR-199a**, *miR-200a*, *miR-100*, *miR-125b*, and *let-7* cluster. They found that *miR-214* induces cell survival and cisplatin resistance through targeting the PTEN 3′-UTR, which leads to downregulation of PTEN protein and activation of Akt pathway.

To identify new pathways that regulate susceptibility to tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) in non-small cell lung cancer (NSCLC), Garofalo et al. (2008) performed genome-wide expression profiling of miRNAs showing that in TRAIL-resistant NSCLC cells, the expression levels of *miR-221/222* are increased. These miRNAs target the 3′-UTR of Kit and p27(kip1) mRNAs, but interfere with TRAIL signaling mainly through p27(kip1), resulting in inhibition of TRAIL-dependent apoptosis and suggesting that high expression levels of *miR-221* and *-222* are needed to maintain the TRAIL-resistant phenotype.

In prostate tumors *miR-34a* expression appeared markedly reduced in *p53* null and *p53*-mutated cell line PC3 and DU145, respectively compared with *p53* wild-type LNCaP cells. In PC3 cells restoration of high levels of *miR-34a* decreased *SIRT1* expression, leading to cell cycle arrest, growth inhibition and attenuated chemoresistance to the anticancer drug camptothecin by inducing apoptosis (Fujita et al., 2008).

However, the role of miRNA in the acquisition of drug resistance by cancer cells still remains elusive and more studies in this direction are warranted.

Molecules which can modulate miRNAs expression

To date little is known about the possibility that some molecules are able to modulate the expression of miRNAs, but some recent studies have considered such an opportunity as a possible novel approach to cancer treatment. Molecules known as miRNAs modulators have been reported in Table 2.

Natural dietary chemopreventive agent

Curcumin is an active component of turmeric which has been studied in combination with gemcitabine in pancreatic cancer cell lines (Kunnumakkara et al., 2007; Lev-Ari et al., 2007) and appears useful in combination therapy especially because it is nontoxic to humans and showed multitargeted effects, including the inhibition of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and cyclooxygenase 2 (COX-2) (Lev-Ari et al., 2007). In additions, it can alone modify the expression of specific miRNAs in pancreatic cancer cells, which could be significant in mediating its biologic effects (Sun et al., 2008). Unfortunately, its limited absorbance across the intestine in humans limits its therapeutic applications. In a recent studys, Ali et al. (2010) have demonstrated that CDF, a synthetic analog of curcumin, is significantly more effective in killing gemcitabine-resistant cells, maybe because of its better cellular uptake and retention. They found that CDF and its combination with gemcitabine could significantly down-regulate the expression of *miR-21* in gemcitabine-resistant pancreatic cancer cell lines MIAPaCa-E and MIAPaCa-M, where *miR-21* expression is upregulated compared with gemcitabine-sensitive BxPC-3 cells. *miR-21* regulates several genes, is overexpressed in several tumors, and is associated with tumor progression, poor survival and reduced therapeutic effects. They found that PTEN, a tumor suppressor gene *miR-21* regulated, was reactivated in cell lines treated with CDF or curcumin. The activation of PTEN would decrease Akt phosphorilation which would contribute to the inhibition of cell growth and induction of apoptosis. Moreover, the expression of other two miRNAs, *miR-200b* and *miR-200c*, which were drastically reduced in gemcitabine-resistant cell lines and either lost or substantially decreased in various tumors, could be upregulated by CDF and curcumin. *miRNA-200* family plays an important role in regulation of epithelial-to-mesenchymal transition (EMT) during tumor development and progression, and is associated with cancer recurrence and overall survival. Reactivation of *miR-200* could then determine the inhibition of EMT with consequent reversion of mesenchymal-like morphology of gemcitabine-resistant cells which regained sensitivity to it.

Hormones

There is some evidence on the ability of estrogen to regulate miRNAs.

Through a microarray approach, Castellano et al. (2009) identified a subset of miRNAs modulated by ER. Among them some miRNAs derived from the processing of the paralogous primary transcripts (pri-) *miR-17-92* and *miR-106a-363* were upregulated. The modulation of the pri-*miR-17-92* by ER appears mediated by the *c-MYC* oncogene by its direct interaction with the *miR-17-92* promoter and this phenomenon is specific to breast cells. They observed that levels of pri-*miR-17-92* increased earlier than the mature miRNAs derived from it, suggesting precursor cleavage modulation occurs after transcription. Pri-*miR-17-92* is

Table 2 miRNAs modulators

Molecule	Target	Up/Downregulation	Chemotherapeutic agent in combination	Tuomor type	Author
Curcumin CDF synthetic analogue	*miR-21*	↓	Gemcitabine	Pancreas	Ali et al., 2010
Curcumin CDF synthetic analog	*miR-200b* *miR-200c*	↑	Gemcitabine	Pancreas	Ali et al., 2010
Estrogen	*miR-17-92* *miR-106a* *miR-363*	↑		Breast	Castellano et al., 2009
Estrogen	*miR-128a*	↑	Letrozole	Breast	Masri et al., 2010
p53 mutated	*miR-34 family*	↓		Ovarian	Corney et al., 2007
p53 wild type	*miR-192* *miR-215*	↑		Ovarian	Georges et al., 2008

instantly cleaved by DROSHA to pre-*miR-18a*, suggesting that its regulation occurs during the formation of the mature molecule from the precursor. The clinical implications of this new regulatory system were demonstrated by the fact that pre-*miR-18a* was significantly upregulated in ERα-positive compared to ERα-negative breast cancers.

Again as part of breast cancer Masri et al. (2010) identified 115 differentially regulated miRNAs in hormone refractory cell lines, 49 of which were believed to be hormone-responsive. Among them they focused their interest on *miR-128a* which was upregulated in letrozole-resistant cell lines and was predicted to target TGFβ signaling pathway, supported by the evidence that sensitivity to TGFβ was compromised in those cell lines when compared to parental MCF-7aro (MCF-7 stably transfected to overexpress the aromatase gene). Inhibition of endogenous *miR-128a* resulted in resensitization of the letrozole-resistant cell lines to TGFβ growth inhibitory effects suggesting that this hormone-responsive miRNA can modulate TGFβ signaling and survival of cell lines resistant to letrozole.

p53

Several studies demonstrated that transcription factor and tumor suppressor p53 directly transactivates genes of the *miR-34* family, which is composed of *miR-34a-34b-34c* members (Bommer et al., 2007; Chang et al., 2007; Corney et al., 2007; Tarasov et al., 2007). This family of miR downregulates several important regulatory proteins and thus presumably mediates tumor suppression (Chang et al., 2007). Interestingly, in a recent study, Corney et al. (2010) found a correlation between decreased expression of *miR-34* and *p53* mutation in epithelial ovarian cancer (EOC). They evaluated the potential role of *miR-34* family determining their expression level in a panel of 83 cancer tissues and found that *miR-34* expression is often reduced in EOC and is correlated with metastatic clinical stage and increased expression of protein tyrosin kinase MET. In EOC cells, a reconstitution of *miR-34* expression leads to reduced proliferation and invasion as well as decreased MET levels.

In addition to *miR-34* family, other miRNAs appear to be involved in coordinating the transcriptional and posttranscriptional responses to p53 activation. Georges et al. (2008) showed that genotoxic stress promotes p53-dependent upregulation of *miR-192/215*. Enforced expression of *miR-192* or *miR-215* leads to G1 and G2-M cell cycle arrest. Using gene expression profiling and RNAi-mediated gene silencing, they identified a set of downstream effectors of *miR-192/215* that includes a number of regulators of DNA synthesis and the G1 and G2 cell cycle checkpoints. By regulating the expression of these key cell cycle genes, *miR-192/215* may mediate the cell cycle arrest function of p53 suggesting that multiple miRNA families operate in the p53 network.

Conclusions

MiRNAs are a class of small non-coding RNAs, physiologically present in humans, that regulate gene expression at post-transcriptional level thus controlling important mechanisms such as development, apoptosis and cell proliferation. MiRNAs are involved in carcinogenesis and are deregulated in several types of cancer. For this reason they have recently begun to be explored as potential diagnostic or therapeutic targets in cancer treatment. Of particular interest is the understanding of a possible association between the expression of these small molecules and adverse events such as the establishment of forms of chemo- and radio-resistance. The evidence of the roles of miRNAs in determing drug sensitivity/resistance has been emerging and extensive studies have indicated that the acquisition of MDR by tumor cells can be modulated by changes in miRNA levels. On the other hand, little is known about miRNAs expression modulators. Modulation of specific miRNAs alterations in cancer can repair the network of gene regulation related to pathways of apoptotic signal or sensitivity to drugs, thereby improving treatment outcomes. Therefore, the development of molecules that interfere with miRNAs represents a future application of considerable pharmaceutical interest because it could be useful for designing novel strategies for the prevention of tumor progression and/or treatment of cancer, using these molecules as alternative chemotherapeutic agents or in combination with standard chemotherapeutic drugs.

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