Published in final edited form as:

Pharmacogenomics. 2012 September ; 13(12): 1321–1324. doi:10.2217/pgs.12.121.

The miRNA–drug resistance connection: a new era of personalized medicine using noncoding RNA begins

Prasun J Mishra

Center for Cancer Research, National Cancer Institute, National Institutes of Health, 37 Convent Drive, Bethesda, MD 20892, USA, Tel.: 301 451 8522, Fax: 301 480 4662, mishrapj@mail.nih.gov

Keywords

diagnosis; disease; drug resistance; epidemiology; genetic variation; genomic medicine; individualized medicine; microRNA; miRNA; miR SNP; mutations; ncRNA; noncoding RNA; personalized medicine; pharmacogenomics; polymorphisms; prognosis

“There will come a time when you believe everything is finished. That will be the beginning...”

– Louis L’Amour [101].

The human genome project, designed to sequence every base pair of the human genome and one of the most ambitious scientific undertakings attempted by mankind, is declared complete [102]. Although completion of sequencing the human genome is a landmark in human history, this does not represent an ending, but rather a new beginning. With an unprecedented knowledge of the more than 3 billion DNA base pair sequences in the whole human genome, we can now focus on identifying and characterizing novel diagnostic and prognostic markers to better treat patients and to make the elusive dream of personalized medicine a reality.

“[ncRNAs] are a promising field of research that holds great potential for individualized medicine. Since the discovery of the first miRNA associated with drug resistance (miR-24), several other miRNAs have been identified to be associated with drug resistance, spanning almost all classes of drugs (450 publications to date), and the list is growing.”

One of the most striking findings that has come out of the human genome project is the prevalence and the importance of the noncoding region that encodes miRNAs. These small ncRNAs [1,2] are predicted to regulate one-third of the human genome [3,4], can be used to help predict drug response [5,6] and are a promising field of research that holds great potential for individualized medicine. Since the discovery of the first miRNA associated with drug resistance, (miR-24) [6], several other miRNAs have been identified to be associated with drug resistance spanning almost all classes of drugs (450 publications to date), and the list is growing [103]. The knowledge of all the miRNAs associated with drug resistance will be a key to designing drugs with greater efficacy and safety, and has significant health and economic implications.

Financial & competing interests disclosure

The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

miRNAs are considered as attractive therapeutic agents, since they may be differentially expressed in malignant versus normal cells [7,8]. However, miRNA re-expression therapy has both advantages and limitations [9]. With the discovery of the role of miRNAs in drug resistance [6], another promising approach has emerged – the use of miRNAs encoded by the human genome as diagnostic tools to predict drug response. Loss of miRNA function could alter the levels of drug targets in a cell and confer drug resistance [6]. For example, miR-24 regulates expression of the *DHFR* gene, the target of an anticancer drug methotrexate, by binding to its 3'-UTR. A SNP in the 3'-UTR of *DHFR* results in an increased expression level of DHFR owing to a loss of the miR-24 function SNP, and was found to be associated with drug resistance [6]. Thus, in addition to gene amplification causing DHFR overexpression [10], loss of miRNA function represents a new mechanism of target overexpression and drug resistance [5,6] and establishes an miRNA–drug resistance link [6]. In a follow-up report, miR-24 was demonstrated to act as a p53-independent tumor suppressor miRNA, and loss of miR-24 function not only confers drug resistance, but also imparts a growth advantage to immortalized cells and induces neoplastic transformation [11]. Thus, recent advances in the miRNA field have led to the understanding of entirely new mechanisms of cellular transformation and drug resistance caused by loss of miRNA function [6,11].

Cumulating evidence now demonstrates that miRNA levels in the cell can be a major determinant of drug sensitivity or resistance. Several groups worldwide have identified miRNAs associated with sensitivity or resistance to many types and classes of chemotherapeutic drugs [103]. Examples linking miRNA with resistance to methotrexate, nogamycin, camptothecin, TRAIL, doxorubicin (DOX), tamoxifen, paclitaxel, cisplatin, vinblastine, hydroxyurea, microtubule-targeting agents, gefitinib, lapatinib, mitoxantrone, interferon and 5-fluorouracil have been reported in the literature. In a recent review, based on the current information within the miRNA field, we have compiled a comprehensive catalogue of human miRNAs associated with drug resistance, sensitivity and pharmacogenomics to better facilitate individualized medicine [Mishra PJ, Humeniuk R. MicroRNA pharmacogenomics and personalized medicine: a comprehensive catalogue of human microRNAs associated with drug resistance, sensitivity and pharmacogenomics to facilitate individualized medicine, Pharmacogenomics (2012), Submitted]. The following are only a few of the many early examples of miRNAs identified to be associated with drug sensitivity/resistance [103].

Two miRNAs, miR-21 and miR-34a, were found to affect the efficacy of the DNA intercalating drugs camptothecin and nogamycin. It was demonstrated that overexpression of miR-21 in three cancer cell lines (A549: non-small-cell lung; SNB-19: glioma; and OVCAR-3: ovarian) conferred chemoresistance to NSC265450 (nogamycin) and NSC67055014 drugs [12]. Other than miR-24, miR-192 [13] and miR-140 [14] were recently shown to be associated with chemoresistance to methotrexate and 5-fluorouracil, respectively.

miR-451 was associated with *mdr1* gene regulation; overexpression of miR-451 in MCF-7/DOX-resistant cells conferred increased sensitivity to DOX [15]. Overexpression of let-7a resulted in downregulation of caspase-3 and conferred DOX resistance in the A431 cell line [16]. MiR-21 was found to be associated with multidrug resistance (DOX and paclitaxel) along with other proteins in a hyaluronan-induced CD44 pathway [17].

miR-130a, one of the miRNAs downregulated in a drug-resistant cell line, targets the *M-CSF* gene, a known resistance factor in ovarian cancer [18]. miR-214 was recently shown to also be associated with ovarian cancer cell survival and cisplatin resistance by regulating PTEN levels (site in 3'-UTR) and consequently activating Akt pathways [19]. miR-15b/

miR-16 were found to be downregulated in the multidrug-resistant human gastric cancer cell line SGC7901/VCR, developed through modulation of BCL2 expression [20].

“To integrate miRNA personalized medicine into clinical practice, researchers, policy-makers, government and pharmaceutical companies need to work together toward characterizing disease and drug response-associated miRNAs as biomarkers, and integrate the knowledge to predict clinical drug response, which will be helpful in overcoming adverse drug reactions.”

Increased expression of miR-221/222 conferred TRAIL resistance and a reduced level of p27 (Kip1) [21]. miR-221/222 were also found to be associated with tamoxifen (antiestrogen) resistance in breast cancer cell lines by regulating p27Kip1 [22] and estrogen receptor α [23]. A computational analysis suggested that miRNAs were deregulated in antiestrogen-resistant MCF-7 cells (estrogen receptor-positive) [24]. Downregulation of miR-27a or miR-451 resulted in an increased intracellular accumulation of vinblastine and hydroxyurea [25]. More recently, miR-27a was found to be associated with poor prognosis with respect to platinum-based chemotherapy in ovarian cancer patients [26]. miR-200c overexpression reduced TUBB3 expression and restored sensitivity to microtubule-targeting anticancer agents [27]. miRNA-125b induced resistance to androgen withdrawal in LNCaP cells by regulating BAK1 (involved in drug-induced apoptosis) [28].

Overexpression of miR-205 was found to downregulate HER3 in SKBr3 human breast cancer cells, and to improve gefitinib and lapatinib chemosensitivity [29]. miR-21 targets LRRFIP1, an inhibitor of NF- κ B signaling, and contributes to VM-26 resistance in glioblastoma cells [30]. Two miRNAs, miR-519c [31] and miR-328 [32], were found to inhibit ABCG2 expression and were associated with drug sensitivity; miR-328 was also associated with mitoxantrone resistance in breast cancer cells [32]. miR-155 was identified as one of the miRNAs that regulates proliferation and growth of Waldenstrom macroglobulinemia cells by inhibiting the MAPK/ERK, PI3K/AKT and NF- κ B pathways, and was associated with poor prognosis with respect to Waldenstrom macroglobulinemia drugs [33]. Individuals with chronic hepatitis C with decreased levels of miR-122 responding poorly to interferon therapy [34]. Most of the above discussed miRNAs can be utilized as prognostic markers for corresponding drugs in the clinic.

Perhaps the brightest future of miRNAs associated with drug resistance can be in facilitating individualized/personalized medicine in the clinic [35]. As discussed above, miRNAs can be major players in contributing to drug resistance. These miRNAs can be used as drug prognostic tools in developing molecular assays to detect the response of drugs and/or tailor their dosage, as well as to provide a personalized therapy or initiate a preventative measure [5]. To integrate miRNA-personalized medicine into clinical practice, researchers, policy-makers, governments and pharmaceutical companies need to work together toward characterizing disease and drug response-associated miRNAs as biomarkers, and integrate the knowledge to predict clinical drug response [36], which will be helpful in overcoming adverse drug reactions.

In conclusion, the completion of the human genome project has marked the beginning of an exciting new era of personalized medicine. miRNAs are emerging as a powerful tool to study the biology of a disease and aid in its diagnosis and prognosis [37]. The knowledge of miRNAs associated with drug response may provide a better understanding of pharmacological response to a drug and will revolutionize drug discovery and the developmental process. A better understanding of the role of miRNAs in drug response will allow the development of a more personalized and/or a population-specific treatment, providing greater degrees of success and helping to make the dream of personalized medicine a reality.

Acknowledgments

This work was supported by the Intramural Research Program of the Center of Cancer Research, NCI, NIH. Author thanks Dr Glenn Merlino, Chief Laboratory of Cancer Biology and Genetics, National Cancer Institute, USA, for the critical review of the manuscript.

Biography

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