

Association of Micro RNA (MiRNA) with Drug Resistance in Malignancies

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Abstract

The resistance against chemotherapy in malignancies is a major challenge in clinical oncology and remarkable successes related to this field have been achieved. Many mechanisms such as gene mutation, oxidative stress, tumor hypoxia, multidrug efflux pumps, DNA methylation and histone modification have important roles in the resistance of cancer cells to chemotherapeutic agents. Recent researches in molecular oncology raised the role of miRNAs on the development of drug resistance in cancers. In this review, we will focus on the updated findings about the interaction between a variety of miRNAs and other cellular molecules that result in drug resistance.

Keywords

miRNAs, Drug resistance; Malignancies; Molecular base

Introduction

Each micro RNA is complementary or partially complementary to one or more of mRNA molecules and its main function is to regulate the gene expression.

MicroRNAs (miRNAs) are a novel class of endogenous short, non-coding RNA molecules of which the mature form is about 22 nucleotides in length. MiRNAs are counted as master regulators of gene expression by either cleaving or binding directly to its 3'-UTR region. Several studies revealed the role of miRNAs in chemo resistance in various malignancies and modulate multiple signaling pathways, adding another mechanism of multi-drug resistance. So that even subtle changes in miRNAs expression can cause significant changes in disease progression and cancer outcome. Depending on the cellular function of miRNAs targets, these molecules could be considered either an oncogene or a tumor suppressor gene [1].

The Role of miRNAs as Predictors of Response or Resistance in Variety of Cancer Types

Thousands of human microRNAs have been identified so far. A single microRNA can potentially target up to 200 mRNAs; and the same mRNA molecule may also be targeted by different microRNAs underlining the wide range and complexity of miRNAs functions [2].

UHRF1 is a gene that codes a protein named E3 ubiquitin-protein ligase and is described as a possible cause of cancer. UHRF1's overexpression, observed in malignancies, is associated with decreased expression levels of several tumor suppressor miRNAs. Therefore, it is supposed that the large quantities of the UHRF1 produced in tumors may be a result of miRNAs expression abnormalities [3]. In medulloblastoma tumors, UHRF1 is regulated by microRNA-378 that modulates cell proliferation and apoptosis and Ectopic expression of UHRF1 rescued miR-378-suppressed cell proliferation [4].

MiR-146a/b was found to be correlated inversely with UHRF1 in human gastric carcinoma (GC) tissues and interfering with this pathway may represent a therapeutic approach for blocking GC metastasis [5].

On the other hand, it is hypothesized that chemo-resistance results from specific miRNAs down regulation. This is mainly because there is a correlation between reduced expression of some miRNAs and upregulation of multiple drug resistance (MDR) proteins. For example, miR-298 directly targets MDR-1 in a dose-dependent manner, resulting in decreased levels of P-glycoprotein, while miR-125b affects the sensitivity to nitrate respiration regulator (DNR) through down-regulating both G protein-coupled receptor kinase 2 (GRK2) and p53-up-regulated modulator of apoptosis (PUMA) which contribute to cell apoptosis by enhancing caspase-3 cleavage. The observation that miRNAs can have contrasting effects on the therapeutic response to the same antineoplastic agent in different tumor types coupled with the association between the differing potency of anticancer agents in the

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same cancer cell and the miRNAs and methylation-modified gene expression during chemoresistance development, indicates that the relationship between the functions of miRNAs and drug resistance is highly complex [6].

In many cancer cell lines, miRNAs have been shown to repress translation of PTEN mRNA by interacting with the 3' untranslated region as observed with miR-21 that represses PTEN expression in many cancer subtypes. Also, it has been found that the transcription factor transforming growth factor beta (TGF- β), which inhibits PTEN expression in some models, up-regulates miR-21 expression [7].

In the light of the liquid biopsy using the circulating RNA for the follow up in cancer progression and treatment the miRNAs are emerging as biomarkers for a variety of cancers notably when resistant to drug evolved.

In Breast Cancer

The following micro RNAs (miR-9, miR-10b, and miR-17-5p) are helpful in disease diagnosis while others, such as miR-148a and miR-335 can be used for prognostic purpose, and for prediction of therapeutic outcomes the following miRNA can be supportive (miR-30c, miR-187, and miR-339-5p). In addition, these miRNAs have important roles in invasion, metastasis, proliferation, apoptosis, and genomic instability. In particular, circulating multiple miRNA profiles are showing better diagnostic and prognostic performance as well as better sensitivity than individual miRNAs in breast cancer. New miRNA-based drugs are also promising therapy for breast cancer (e.g., miR-9, miR-21, miR34a, miR145, and miR150), and other miRNAs are showing a fundamental role in modulation of the response to other non-miRNA treatments, being able to increase their efficacy (e.g., miR-21, miR34a, miR195, miR200c, and miR203 in combination with chemotherapy) [8].

MiRNAs may provide an improved understanding of the underlying resistance mechanism as compared to the currently established biomarkers. Examples of miRNAs involved in the switch to alternative ER-independent pathways are miR-10a, miR-126, and miR-30c that are related to PI3K signaling. MiRNAs involvement in tamoxifen resistance, cell proliferation and invasion is effectuated by miR-210 overexpression, while cell survival is promoted by a decrease in miR-26a, and angiogenesis is stimulated by elevation of miR-126. MiR-17/20 increases tamoxifen sensitivity and reduces doxorubicin resistance in MCF-7 breast cancer cells [9], whereas upregulation of miR-218 sensitized MCF-7 cells to cisplatin. MiR-27b regulates tamoxifen sensitivity by targeting HMGB3 and it is epigenetically down-regulated in tamoxifen resistant breast cancer cells through promoter methylation. On the other hand, overexpression of miR-200c or blockage of the TGF β signaling synergistically promoted trastuzumab sensitivity [10]. In approximately 30% of ER+ breast cancer patients, endocrine treatment fails due to tamoxifen resistance. In breast cancer cells (MCF-7 and MDA-MB-231) IGF-I signed up-regulates-in a time and dose dependent manner-DDR1 collagen receptor by suppressing MIR-199a-5p through the PI3K/AKT pathway.

In addition, the miR-195 and miR-196a are up-regulated in breast cancer, and recently, miR-195 has been identified as a serum biomarker for diagnosis and follow up in breast cancer patients. On the other hand, miR-494 and miR-141 can suppress the progression of breast cancer cells by repressing β -catenin expression. Besides, miR-375 is down-regulated in MCF-7/ADM and MCF-7/PTX cells due to promoter methylation. MiR-375 can directly target 3'UTR of YBX1 and thereby decrease its expression, which might be an important mechanism of MDR in breast cancer cells [11].

In Hepatocellular Carcinoma (HCC)

It was noticed that the over-expression or silencing of ATP-binding cassette B1 (ABCB1) can rescue the antineoplastic therapy cell response that is mediated by miR-223 overexpression or inhibition, respectively. Therefore, miR-223 may be considered as a therapeutic biomarker for HCC patients who had MDR problems induced by high expression of ABCB1 [12,13].

In Colorectal Cancer (CRC)

MiRNAs have been described to play a major role in CRC. All of miR-9, 578, 200c, 451, 302a, 125a/b, and 147 carry the potential of being a therapeutic target. MiR-9 acts as tumor suppressor and its expression has been observed to be decreased in CRC compared to the corresponding normal tissues [14].

MiR-587 has been described as a causative factor of 5-FU resistance in colorectal cancer mainly through decreasing the inhibitory effects of 5-fluorouracil (5-FU) on tumor growth and causing resistance to the 5-FU induced apoptosis. MiR-302 has been described as target gene to regulate 5-FU induced autophagy in CRC cell lines [15,16]. In addition, upregulating miR-302a suppresses CRC invasion and progression mainly through inhibiting the PI3K/Akt and MAPK signaling pathways [15-17].

MiR-200c is an oncomiR that is usually up-regulated in CRC. It enhances Epithelial-to-Mesenchymal Transition (EMT) and promotes the consequent metastatic activity. High levels of miR-200c have been reported in CRC patients with liver, lymph node, and other metastases [17-19].

Besides, MiR-451 is notably down-regulated in the HCT116 and HT 29 colon cancer cell lines. Its expression is inversely correlated with colon cancer Dukes stage [18-20].

Miyazaki *et al.* [21] reprogrammed DLD-1 colon cancer cell lines by introducing miR-302a through lipofection. This led to an increased sensitivity to 5-FU treatment, potentially due to miR-302a downregulation of multidrug-resistant MDR protein.

MiR-125a/b is usually silenced in ALDH1-positive HT29 and HT29-taxol colon cancer cells. Upregulating miR-125a/b suppresses ALDH1A3 and Mcl1 expression [22]. This, in turn, augments cell apoptosis in HT29-taxol cells and decreases their survival. Injecting miR-125a/b expression vector suppresses tumor growth in xenograft HT29-taxol mouse model, which brings about a possible role for miR-125a/b in paclitaxel-resistant colon cancer [20,22].

miR-147 reversed HCT116 (cell line) native resistance to gefitinibe (An EGFR inhibitor). These findings clearly highlight the possible antineoplastic effects of miR-147 on colon cancer cells [23].

In Lung Cancer

Miro RNAs play a main modulating role in lung cancer. All of Mir-200, 34a, 21, 221/222, 30b/c, 103, 203, 200b, 206, 193a-3p, and let-7c act as mentioned either oncomiRs, chemotherapy resistance inducers or tumor suppressors and are thus possible therapeutic targets in the future [24,25].

MiR-200 family members (miR-200s) serves an important role in combating tumor cell invasion, EMT and metastasis and are frequently silenced in advanced lung cancer. The miR-200 family has the potential to become a novel class of biomarker for tumor prognosis and targets of novel drugs against tumor progression [25-26].

A correlation between EGFR expression and post-gefitinibe therapy survival has been established. In EGFR mutant NSCLC, miR-34a overcomes hepatocyte growth factor (HGF) -mediated gefitinibe resistance by targeting MET. Another study showed that miR-21 over-expression was associated with acquired resistance to TKIs in NSCLC [24-27].

On the other hand, miR-221/222 and miR-30b/c induces resistance to gefitinibe by targeting APAF-1 and BIM while miR-103 and miR-203 act as tumor suppressors in lung cancer, inducing sensitivity to TKIs and mesenchymal-epithelial transition by targeting Protein Kinase C ϵ (PKC- ϵ) and tyrosine-protein kinase Src (SRC). Another inducer of drug resistance is hedgehog signaling which plays a major role in lung cancer drug resistance as well [27]. Inhibition of this pathway using siRNAs increased the response of NSCLC cells to erlotinib through the up-regulation of two important tumor suppressor miRNAs, miR-200b and let-7c [27,28].

It has been shown that miR-206 directly targets c-Met and inhibits its downstream PI3k/Akt/mTOR signaling pathway. In contrast, miR-

206 inhibitors promote the expression of c-Met and activate the PI3k/Akt/mTOR signaling, and this effect could be attenuated by the PI3K inhibitor.

Also, mir-206 acts as a tumor suppressor able to inhibit the expression of proto-oncogenes c-Met and Bcl2 that are overexpressed in various cancers including lung cancer. MiR-206 showed inhibitory effects on EMT and angiogenesis in xenograft tumor mice model. Also, it inhibits HGF-induced EMT and angiogenesis in lung cancer by suppressing c-Met/PI3k/Akt/mTOR signaling. Thus, miR-206 might be a potential target for the therapeutic strategy against EMT and angiogenesis in lung cancer [29].

Repression of ERBB4 by miR-193a-3p suppresses proliferation, invasion and promote apoptosis in lung cancer cells and this miR-193a-3p exerts an anti-tumor effect by negatively regulating ERBB4 in xenograft mice.

Moreover, miR-193a-3p is considered as a tumor suppressor in NSCLC through the inhibition of ERBB4 translation.

Nonetheless, it has been recently observed that miR-193a-3p represses the metastasis of lung cancer by targeting several highly expressed proteins in NSCLC including UHRF1 [24-30].

In Prostate Cancer

Prostate cancer (PCa) is a leading cause of male cancer-related deaths. It has a worse prognosis in black males than Caucasians. Further, PCa is associated with high rates of recurrence, and often attributed to the existence of cancer stem cells. A significant fraction of prostate tumors are very aggressive, often metastasizing to the bone, and causing significant morbidity and mortality. Epithelial-mesenchymal transition (EMT) plays a major role, particularly in the context of metastatic disease and microRNAs have emerged as critical post-transcriptional regulators of prostate cancer EMT [31-33].

Treating castrate-resistant prostate cancer (CRPC) is a real challenge that limited the treatment of metastatic castrate-resistant prostate cancer (mCRPC). Typically, the treatment is a docetaxel-based chemotherapy. Resistance to chemo drugs has been associated with inhibition of tumor suppressive miRNAs and expression of oncogenic miRNAs. This wide variety of miRNAs has the potential to be therapeutically targeted to overcome chemotherapy resistance and improve patient survival. Some of these miRNAs include miR-375, miR-21, miR-222, miR-221, miR-205, miR-200b, miR-466, miR-24, miR-200b, miR-30, miR-3622b, Runx-targeting miRNAs, miR-138, miR-573, and miR-34a [34-36].

In regard to miR-375, the overexpression of miR-375 in prostate cancer tissues is associated with poor overall survival of mCRPC patients [37].

On the other hand, MiR-21 is an oncomiR that is up-regulated in prostate cancer. MiR-21 overexpression enhanced tumor growth and imparted castration resistance by driving androgen-dependent tumors to surpass androgen mediated growth arrest. Furthermore, suppressing miR-21 with antisense oligonucleotides in androgen-independent prostate cancer cell lines DU145 and PC-3 increased apoptosis sensitivity along with inhibiting cell motility and invasion probably due to its regulatory activity on PDCD4, TPM1, and myristoylated alanine-rich protein kinase substrate (MARCKS). MiR-21 directly targets MARCKS and promotes apoptosis resistance and invasion in prostate cancer cells [38].

MiR-222 & miR-221 play a controversial role in PCa. They have been described as tumor suppressor genes that inhibit migration and invasion and are down-regulated in prostate cancer and castration resistant prostate cancer (CRPC) cell lines. On the other hand, they have been described as oncomiRs that promote cell proliferation and suppress apoptosis. Knocking down these miRNAs led to an increased sensitivity of prostate cancer cells to TNF- α /CHX-induced apoptosis. They have also been described as androgen receptor-repressed genes that are down-regulated in response to androgen deprivation therapy (ADT). This, in turn, temporarily increased the cell growth potential of PCa [39,40].

miR-205 is a very valuable therapeutic target in PCa to overcome

chemotherapy resistance. MiR-205 is another miRNA that plays a major role in the radiosensitivity of prostate cancer cells. It sensitizes PCa cells to radiotherapy and suppresses radiotherapy induced autophagy. MiR-205 is also linked to docetaxel resistance and EMT. Re-expression of MiR-205 led to increased Docetaxel sensitivity and toxicity in PCa mainly through shifting the metabolic pattern to Warburg metabolic pattern. Furthermore, miR-205 replacement increased cisplatin sensitivity and decreased autophagy. In general, miR-205 is down-regulated in PCa chemotherapy-resistant cell lines, where increasing its expression sensitized these cells to chemotherapy mainly through enhancing chemotherapy-induced apoptosis [41].

Likewise, miR-466 levels can discriminate between malignant and normal prostate tissues, and can predict biochemical relapse. It is strongly suggested that miR-466-mediated attenuation of RUNX2 can be used as a novel therapeutic approach to regulate PCa growth, particularly PCa metastases to bone.

In addition to that, MiR-24 is a miRNA that is differentially expressed in African American and Caucasian American PCa patients. It may be a central regulator of key events that contribute to race-related PCa tumorigenesis and it has the potential to be a therapeutic agent for PCa treatment [42-44].

Interestingly, in prostate stroma, active vitamin D (1, 25 (OH) 2D) modulates and regulates expression of the following miRNAs -miR-126-3p, miR-154-5p and miR-21-5p- that have been proven to be involved in chemotherapeutic resistance [45].

PCa development is reinforced by the TMPRSS2-ERG fusion that occurs in approximately 50% of prostate cancers (PCa), resulting in expression of the oncogenic ERG in the prostate. ERG is a transcriptional activator with miR-200b/a/429 as its target gene. This implicates an important role for miR-200b in TMPRSS2/ERG-dependent PCa development. Although induction of the tumor suppressive miR-200b subfamily by oncogenic ERG appears to be counter intuitive, it is consistent with the observation that the vast majority of primary prostate cancers are slow-growing and indolent [45,46].

MiRNAs-30 family is another miRNA group that relates to prostate carcinoma. Kumar B et al. [47] described miR-30 family members as direct androgen (AR) inhibitors. Suppressing miR-30b-3p and miR-30d-5p enhanced AR expression and androgen-independent cell growth. Hence, miR-30d-5p levels were inversely correlated with AR activity, as measured by PSA mRNA, in metastatic CRPC.

Runx is a tumor suppressor gene controlled by miRNAs. The loss of Runx-targeting miRNAs (miR-23b-5p, miR-139-5p, miR-205-5p, miR-221-3p, miR-375-3p, miR-382-5p, and miR-384-5p) contributes to aberrant Runx expression in prostate tumors. This Runx/miRNA interaction axis is centered on PTEN-PI3K-AKT signaling pathway indicating that tumor suppressor phenotype of PCa results from activating PTEN through miR-4534 depletion [48-52].

Additionally, low miR-3622b expression was found to be associated with tumor progression and poor biochemical recurrence-free survival. Thus, miR-3622b expression is a promising prostate cancer diagnostic biomarker that exhibits 100% specificity and 66% sensitivity. Restoration of miR-3622b expression in PCa cell lines led to reduced cellular viability, proliferation, invasiveness, migration and increased apoptosis. MiR-3622b overexpression in vivo induced regression of established prostate tumor xenografts indicating the therapeutic potential for this miRNA [37].

It was observed that one aspect of response to chemotherapy in prostate carcinoma was modulated by miR-138 which specifically targeted K2 and inhibited its expression; thereby miR-138/K2/ β 1-integrin signaling axis regulates chemotherapy sensitivity in PCa and mCRPC. Thus, these data identify a novel signaling axis where K2 in combination with chemotherapeutics provides a new target for the treatment of mCRPC [53].

MiR-573 plays a modulatory role in PCa as it controls the activation of FGFR1-downstream signaling in response to fibroblast growth factor 2 (FGF2). Notably, GATA3 directly increases miR-573

expression, and thus down-regulates FGFR1 expression, EMT, and invasion of PCa. This supports the involvement of GATA3, miR-573 and FGFR1 in controlling the EMT process during PCa metastasis [37,54,55].

Similarly, miR-34a induced apoptosis in PCa cells, and a form of non-canonical autophagy that is independent of Beclin-1, ATG4, ATG5 and ATG7. This happens mainly through the downregulation of PCa growth-associated targets like MET, Axl and c-Myc. MiR-34a-induced autophagy and apoptosis resulted in PCa growth inhibition. These combined effects of autophagy and apoptosis are responsible for miR-34a-mediated prostate tumor growth inhibition, and have translational impact, as this non-canonical form of autophagy is tumor inhibitory. Together, these results provide a new understanding of the biological effects of miR-34a and highlight the clinical potential for miR-34a delivery as a treatment for bone metastatic prostate cancer.

Besides, miR-34a is implicated in epithelial-mesenchymal transition (EMT) and cancer stem cells. Lymphoid enhancer-binding factor-1 (LEF1) is a key transcription factor in the Wnt signaling pathway, and has been suggested to be involved in regulation of cell proliferation and invasion. MiR-34a and LEF1 cooperatively regulate prostate cancer cell invasion. It is strongly suggested that miR-34a/LEF1 regulation of EMT plays an important role in prostate cancer migration and invasion. Thereby, the miR-34a-LEF1 axis represents a potential molecular target for novel therapeutic strategies in prostate cancer [56-58].

Conclusion

MiRNAs play very important role in the development of drug resistance in a variety of malignancies, and the expressions of miRNAs in chemoresistant cancer cells could be represented as an oncogene or a tumor suppressor gene.

Alteration the expression of miRNA may have significant implications for therapeutic strategies pointing to overcome cancer cell resistance.

Modulating MiRNAs is going to be the ideal and big promise that can be used or added to the regimen of cancer treatment particularly when resistance arises. However, most observations and investigations that have been accomplished in regard to miRNAs research so far were conducted in vitro and through animal studies. Though, due to advancement in molecular medicine and moving forward to use liquid biopsy more often, the recommendations have been addressed for measuring certain miRNAs in peripheral blood for diagnostic, prognostic and follow up purposes.

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