

Review

Roles of microRNAs in the resistance to platinum based chemotherapy in the non-small cell lung cancer

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Abstract

Platinum-based adjuvant chemotherapy improves survival among patients with lung tumors, in particular non-small cell lung cancer (NSCLC). But the predicament of drug resistance in NSCLC patients is frustrating us. The profiles of microRNAs are different between platinum chemotherapy resistant and sensitive NSCLC cells. Researches regarding microRNAs and their targets, in platinum drug resistant cases, illuminate novel ideals for platinum-based chemotherapy for NSCLC patients. Therefore, in this review we will focus on three aspects: Epithelial-mesenchymal transition (EMT), cell proliferation and apoptosis, and the roles of microRNAs in cisplatin (CDDP) and carboplatin (CBP) resistance.

Key words: microRNAs; platinum drugs; cisplatin; carboplatin; drug resistance; non-small cell lung cancer

Introduction

Non-small cell lung cancer (NSCLC), as its name suggests, refers to all types of lung cancers except small cell lung cancer (SCLC). NSCLC encompasses the majority of lung cancers, and is the leading cause of cancer related deaths worldwide¹. For NSCLC patients in clinical stage II-III with completely surgical removal of tumor, adjuvant cisplatin (CDDP, cis-diammine-dichloro-platinum (II)) based chemotherapy is recommended, when driver mutation hasn't been detected¹. CDDP, approved by the FDA in 1978, is a traditional cytotoxic chemotherapy drug for types of solid tumors, especially NSCLC². It forms cisplatin-DNA adducts to destroy functions of DNA leading to the cytotoxicity³. Unfortunately, CDDP resistance constitutes the current therapeutic plateau which needs to be overcome. This drug resistance is classified into two types: primary resistance which refers to chemoresistance before chemotherapy, and acquired resistance which occurs after chemotherapy². Dysregulations of drug transport and/or metabolism, targeting oncogenes and inhibited drug-induced apoptosis are common mechanisms of drug resistance⁴. Carboplatin (CBP) is the second

generation platinum medicine which is cis-diammine (1, 1-cyclobutanedicarboxylatoplatinum (II)), and produces less ototoxicity and nephrotoxicity¹. Unfortunately, there is cross resistance between CDDP and CBP. Though CBP is also widely used in NSCLC, the primary and secondary resistance to it still confounds patients and doctors. Oxaliplatin is [(1R, 2R)-cyclohexane-1, 2-diamine] (ethanedioato-O, O') platinum (II), and it's often used to treating colorectal cancer². Nedaplatin is cis-diammine-glycolate-O, O'-platinum (II)². However, there is little researches regarding these two drugs resistance to NSCLC, therefore we will not discuss these platinum medicines in this article.

MicroRNAs are endogenous small non-coding RNAs, usually 20-22nt. This class of RNA regulates numerous biological processes via negatively regulating RNA expression⁵. Recently, scientists have demonstrated that microRNAs modulate drug resistance in many such as diffuse large B cell lymphoma and gastric cancer⁶⁻⁷. Prior most researches have also demonstrated the roles of microRNAs in the NSCLC drug resistance. Our team has summarized microRNAs that modulate NSCLC-targeted

treatments, and found that different microRNAs could exert opposite influence in certain target medicine clinical pharmacotherapy⁸. In this review, we discuss the roles of microRNAs in platinum agent resistance and also the possible mechanisms, which provide us a new point of penetration to improve treatments of NSCLC, especially for patients without indications for targeted medicine like EGFR-TKIs (epidermal growth factor receptor-tyrosine kinase inhibitors).

CDDP resistance

According to the latest clinical guidelines for the treatment of NSCLC, CDDP-based chemotherapy is recommended for the majority of early stage and all advanced NSCLC patients without ALK/EGFR mutation¹. Nevertheless the efficacy is impeded by primary resistance, or acquired resistance which usually occurs early. Recent studies have demonstrated that silencing or activating certain miRNAs could reverse drug resistance through different mechanisms.

CDDP resistance and epithelial-mesenchymal transition (EMT)

EMT indicates the phenotypical alterations that occur when epithelial cells lose the epithelial characteristics such as the polarization and cell junctions, and acquire mesenchymal phenotypes⁹. In recent studies, EMT is found to be closely related with chemoresistance rather than metastasis in solid tumors like lung cancer and pancreatic cancer⁹⁻¹⁰. Moreover, a study in oral squamous cell carcinoma (OSCC) has revealed that some miRNAs modulate CDDP resistance partially through regulating EMT¹¹. In NSCLC, microspherule protein 1 (MCRS1), specifically negatively regulated by miR-129* (miR-129-1-3p), induces EMT and CDDP resistance, through increasing the expression of miR-155¹². Paolo Ceppi et al. found that miR-200c inhibited CDDP and cetuximab resistance, with a significant increase of E-cadherin and a decreased of N-cadherin expression which plays an important role in regulating EMT¹³. There is evidence that miR-17 family (-17, 20a, 20b), through negatively regulating TGF-beta receptor type-2(TGFbR2), induces EMT and CDDP resistance¹⁴.

MiR-15b, directly targeting phosphatidylethanolamine-binding protein 4(PEBP4), can both promote CDDP resistance and EMT¹⁵. Raf Kinase Inhibitory Protein (RKIP), targeted by mir-27a can inhibit EMT and CDDP resistance¹⁶. MiR-181a, which is remarkably upregulated in the CDDP-resistant A549 cell line than in the parental cell line, promotes EMT by targeting phosphatase and tensin homolog deleted on chromosome 10 (PTEN), but the role of

miR-181a in CDDP resistance will not be discussed in this study¹⁷. Interestingly, in another study, PTEN, targeted by mir-92b could suppress CDDP-induced apoptosis¹⁸. Taken together, EMT may directly contribute to CDDP resistance via PTEN. (MicroRNAs and their targets mentioned before are summarized in Table 1).

In conclusion, EMT is an important factor in the biological behaviors of miRNAs regulating CDDP resistance in NSCLC, and provides a novel future for treatments of CDDP resistant patients. Nevertheless, this hypothesis needs more supporting evidence.

Table 1. miRNAs involved in CDDP resistance and EMT in NSCLC

| MiRNAs | Targets | Targeted by | References |
|-------------------------------|--|-------------|------------|
| MiR-129*(miR-129-1-3p) | MCRS1 | / | [12] |
| MiR-155 | / | MCRS | [12] |
| MiR-200c | E-cadherin, N-cadherin [#] | / | [13] |
| MiR-17 family (-17, 20a, 20b) | TGFbR2 | / | [14] |
| MiR-15b | PEBP4 | / | [15] |
| MiR-27 | RIKP | / | [16] |
| MiR-181a | PTEN | / | [17] |

[#]: MiR-200c restored E-cadherin expression¹³;*: MiR-129* indicates miR-129-1-3; /: no mention in the references.

Cisplatin resistance and cell proliferation

Uncontrolled cell proliferation is one of the important classic characteristics of tumors. We want to illuminate whether some miRNAs achieve the resistance or opposite effects through acting on cell cycle. Jian Zhao et al. have found that miR-17 family (-17, 20a, 20b) arrests cell cycle at G1/S phase through inhibition of CDKN1A, and miR-17 family can reverse CDDP resistance¹⁹. Additionally, expressions of miR-17 and miR-92 families are related to responses of patients to CDDP treatments without deeper investigations¹⁹. MiR-217, inhibiting cell proliferation, reverses CDDP resistance through targeting Kirsten rat sarcoma viral oncogene homolog (KRAS) gene²⁰. MiR-26a, which is down-regulated in CDDP-resistant A549 cell lines, promotes cell sensitivity to CDDP through inhibiting cell growth by targeting the High Mobility Group A 2(HMGA2)-mediated E2F1-Akt pathway²¹. P53 directly modulates miR-34a, and in turn miR-34a contributes to the p53 network for tumor suppression especially inhibiting tumor cell proliferation²²⁻²⁴. PEBP4, targeted by miR-34a, could promote CDDP resistance, meanwhile PEBP4 can inactivate p53²⁵. In short, it will re-sensitize CDDP-resistant in NSCLC to CDDP when activating the p53/miR-34a loop. Further investigations into the pharmacological mechanisms are still ongoing.

MiR-1 reverses CDDP resistance via inhibiting

SDF-1 and CAFS on cell proliferation²⁶. And miR-138 targets cyclin D3 (CCND3) to regulate cell proliferation²⁷. (MicroRNAs and their targets mentioned previously are summarized in Table 2).

In summary, microRNAs could influence tumor cell proliferation to promote or reverse CDDP resistance. These microRNAs and their targets provide novel insights for treatments and prognostic predictions.

Table 2. miRNAs involved in CDDP resistance and cell proliferation in NSCLC

| MiRNAs | Targets | Targeted by | References |
|-------------------------------|----------------------------------|-------------|------------|
| MiR-17 family (-17, 20a, 20b) | CDKN1A | / | [19] |
| MiR-217 | KRAS | / | [20] |
| MiR-26a | HMGGA2-mediated E2F1-Akt pathway | / | [21] |
| MiR-34a | PEBP4 | P53 | [22][25] |
| MiR-1 | SDF-1, CAFS | / | [26] |
| MiR-138 | CCND3 | / | [27] |

/: no mention in the references.

CDDP resistance and cell apoptosis

Apoptosis is the progression of cell-programmed death and naturally suppresses tumor progression²⁸. Though defects in apoptosis of tumor cells contribute to drug resistance, resulting in the failure of anti-cancer therapy, multiple microRNAs have been demonstrated to participate in cell apoptosis²⁹⁻³⁰. Better understanding of correlations between microRNAs and apoptosis in NSCLC may provide basic principles to improve current therapies.

The cellular uptake of CDDP as a cytotoxic chemotherapy drug triggers some cellular pathways and causes cytotoxic effects³. The ATP-binding cassette (ABC) transporter superfamily is regarded as the largest transporter family, encompassing seven subfamilies (ABCA~ABCG). Previous studies have found ABCB and ABCC subfamilies are involved in multiple drug resistances⁴. Also, several miRNAs can regulate certain ABC transporters which influence CDDP influx or efflux to impair CDDP-induced apoptosis in NSCLC. ABCB9 works as a drug transporter, while miR-31 induces ABCB9 mRNA degradation to decrease CDDP-induced apoptosis through decreased CDDP uptake³¹. Let-7c can reverse CDDP resistance by targeting ABCC2³². Additionally, ABCA1, targeted by miR-106a, can transport CDDP into cells³³.

Besides drug transporters, miRNAs also target other signals to induce or inhibit apoptosis of NSCLC cells. Apoptotic pathways are commonly classified into intrinsic and extrinsic pathways. Bcl-2 family members participate in the intrinsic apoptotic pathway, and different members may have opposite

functions³⁰. MiR-503 and miR-497 target the anti-apoptotic Bcl-2 gene to reverse CDDP resistance³⁴⁻³⁵, and conversely miR-21 decreases expression of anti-apoptotic Bax and increases pro-apoptotic Bcl-2 resulting in re-acquiring CDDP sensitivity³⁶.

Decreased miR-184 could confer CDDP resistance via enhancing Bcl-2³⁷. Bim is a member of the Bcl-2 family that as the opposite effect of Bcl-2. The intrinsic apoptotic pathway relies on the apoptosome, composed of apoptotic protease activating factor 1 (Apaf-1), cytochrome c and procaspase-9³⁰. MiR-155 targeting Apaf-1 and miR-137 targeting caspase-3(CASP3) promote CDDP resistance in lung cancer³⁸⁻³⁹. Mir-940 and mir-92b could suppress CDDP-induced apoptosis by respectively targeting mitogen-activated protein kinase phosphatase-1 (MKP1) and *PTEN*^{18, 40}. MiR-138, in addition to the functions in cell cycle discussed before, also could promote CDDP-induced apoptosis by targeting (excision repair cross-complementation group 1) ERCC1⁴¹.

EGCG enhances CDDP efficacy in apoptosis in NSCLC by inhibiting miR-98-5p⁴²⁻⁴³. MiR-218 can reverse CDDP resistance by decreasing runt-related transcription factor 2(RUNX2)⁴⁴. MiR-1244 may enhance CDDP resistance probably by targeting TP53⁴⁵. MiR-196a may confer CDDP resistance via inhibiting apoptosis probably by targeting human multiple drug resistance 1 (MDR1), multidrug resistance protein 1 (MRP1), excision repair cross-complementation 1 (ERCC1), survivin, and B cell lymphoma 2 (Bcl-2)^{46, 47}. (MicroRNAs and their targets mentioned previously are summarized in Table 3).

Table 3. miRNAs involved in CDDP resistance and apoptosis in NSCLC

| MiRNAs | Targets | Targeted by | References |
|-----------|---------------------------------|-------------|------------|
| MiR-31 | ABCB9 | / | [31] |
| Let-7c | ABCC2 | / | [32] |
| MiR-106a | ABCA1 | / | [33] |
| MiR-503 | Bcl-2 | / | [34] |
| MiR-497 | Bcl-2 | / | [35] |
| MiR-21 | Bax | / | [36] |
| MiR-184 | Bcl-2 | / | [37] |
| MiR-155 | Apaf-1 | / | [38] |
| MiR-137 | CASP3 | / | [39] |
| Mir-940 | MKP1 | / | [40] |
| MiR-92b | <i>PTEN</i> | / | [18] |
| MiR-138 | / | EERCC1 | [41] |
| MiR-98-5p | EGCG | / | [42][43] |
| MiR-218 | RUNX2 | / | [44] |
| MiR-1244 | TP53 | / | [45] |
| MiR-196 | MDR1,MRP1,ERCC1,survivin, Bcl-2 | / | [46] [47] |

/: no mention in the references.

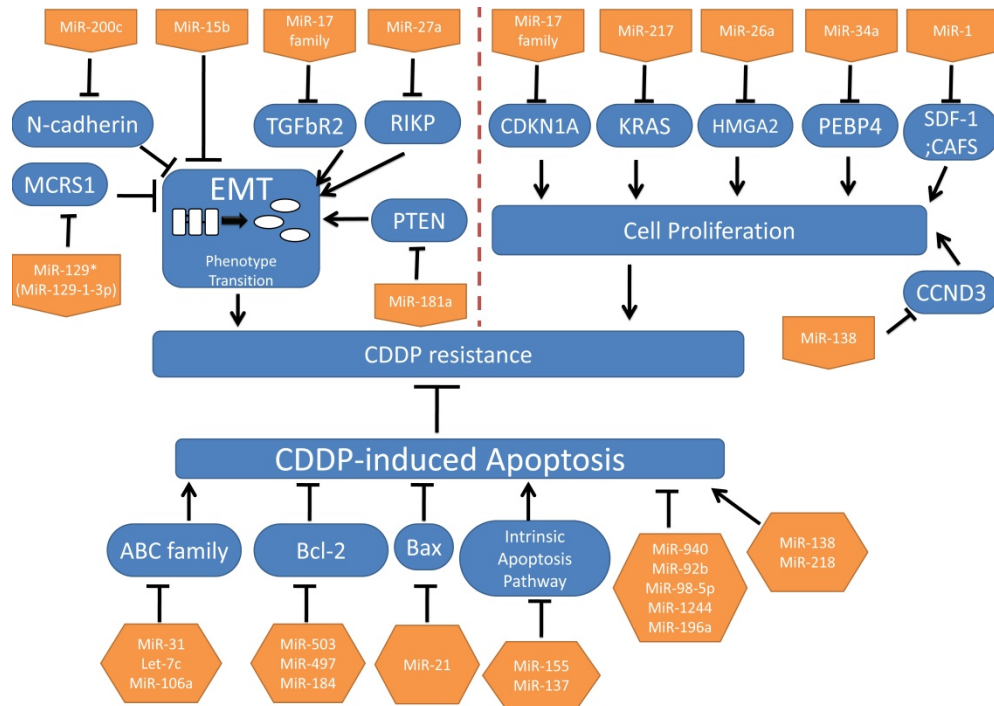


Figure 1. MicroRNAs involved in CDDP resistance in NSCLC.

In conclusion, we primarily summarized microRNAs that appear to be important in CDDP resistance from different biological processes: EMT, cell proliferation and apoptosis. (These microRNAs are summarized in Figure 1.)

Carboplatin(CBP)

There are similar anti-tumor mechanisms between CDDP and CBP, which has fewer side-effects to the kidneys and nervous system⁴⁸. There're few researches regarding microRNAs and CBP in lung cancers. Only miR-218 and miR-205 were found to have opposite functions in CBP resistance in NSCLC⁴⁹. MiR-218 reverses CBP resistance by stimulating apoptosis and cell cycle arrest, while miR-205 promotes cell proliferation to achieve the inverse effects⁴⁹.

In ovarian cancer, miR-21, miR-214, miR-193b, miR-200c and miR-141 were related with platinum resistance⁵⁰⁻⁵². MiR-21 and miR-214 were over-expressed in the ascites cells which were resistant to CBP therapy compared to omental metastases⁵⁰, while miR-21 was found to be inhibited by carboplatin and increase the cell invasion. Further studies on miR-193b, miR-200c and miR-141 show these miRNAs conferred resistance to CBP in ovarian cell lines⁵¹⁻⁵².

In breast cancer, miR-664b-5p increases CBP with gemcitabine sensitivity via targeting CCNE2⁵³. MiR-222/ 223 in mesenchymal stem cell-derived

exosome increases CBP resistance which needs further research⁵⁴. MiR-621 sensitizes breast cancer cells to PTX/CBP by inhibiting FBXO11 and activating p53⁵⁵. Patients with over-expressed miR-659-3p predicted complete or partial response to CBP/ paclitaxel-based treatments⁵⁶.

Although little attention was paid to the roles of miRNAs in CBP resistant NSCLC (from Figure 2) they may be important in predicating CBP sensitivity and acting as a novel targeting mechanism for reversing resistance.

Conclusion

Lung cancer is usually recognized late and is prevalent in cancer related death. NSCLC contributes for the most of lung cancer, and the majority of NSCLC patients are recommended CDDP-based chemotherapy, but CDDP resistance occurs sooner than anticipated. Therefore, we aim to find a new method to reverse CDDP and/or CBP resistance to assist NSCLC patients.

MicroRNAs operate numerous biological signal pathways through negatively modulating expressions of targeted genes. Researchers have demonstrated the importance of microRNAs in CDDP resistance in NSCLC patients. In this review, we classified functions of microRNAs in CDDP resistance into three classes: Class A microRNAs regulate both CDDP resistance and EMT in NSCLC, like miR-129*(miR-129-1-3p), miR-200c, miR-17 family

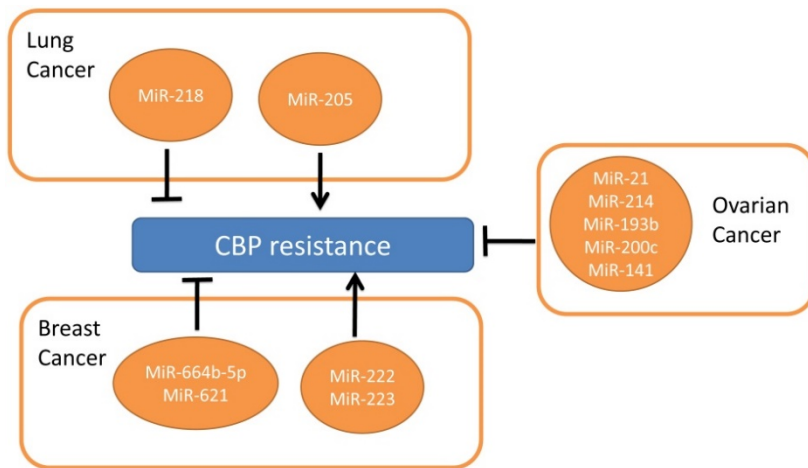


Figure 2. MicroRNAs involved in CBP resistance.

(-17, 20a, 20b), miR-15b, miR-27 and miR-181a¹²⁻¹⁷; Class B includes microRNAs which regulate cell proliferation to contribute to CDDP resistance or sensitivity, such as the miR-17 family (-17, 20a, 20b), miR-217, miR-26a, miR-34a, miR-1, miR-26a, and miR-138^(19-23,25,26-27); Class C contains CDDP resistance related microRNAs which coordinate apoptosis of NSCLC cells, such as miR-31, Let-7c, miR-106a, miR-503, miR-497, miR-21, miR-184, miR-155, miR-137, miR-940, miR-92b and miR-138, miR-98-5p, miR-218, miR-1244, and miR-196^{18,31-38,40-45}. Distinctions between the three classes are not absolute: for example, miR-34a reverses CDDP resistance and inhibits EMT, but also inhibits cell proliferation²²⁻²⁵.

Regarding CBP resistance in NSCLC, miR-218 and miR-205 are the only two microRNAs we found in studies which have opposite roles in CBP resistance⁴⁹, while microRNAs functions in CBP resistance in other tumors are widely studied. There are bright prospects for the study and utilization of microRNAs in reversing CBP resistance.

Overall, further understanding of microRNAs and their targets in CDDP and CBP resistance may contribute to NSCLC treatments. Safely and efficiently increasing the expression of advantageous microRNAs and decreasing expression of disadvantageous microRNAs, although challenging, may provide welcome developments through further study of their targets and mechanisms.

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Ethical approval

This article does not contain any studies with

human participants or animals performed by any of the authors.

Competing Interests

The authors have declared that no competing interest exists.

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