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Interactions between anticancer active platinum complexes and non-coding RNAs/microRNAs

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ABSTRACT

Platinum(II) complexes such as cisplatin, carboplatin and oxaliplatin are clinically approved for the therapy of various solid tumors. Challenging pathogenic properties of cancer cells and the response of cancers towards platinum-based drugs are strongly influenced by non-coding small RNA molecules, the microRNAs (miRNAs). Both increased platinum activity and formation of tumor resistance towards platinum drugs are controlled by miRNAs. This review gives an overview of the interactions between platinum-based drugs and miRNAs, and their influence on platinum activity in various cancer types is discussed.

1. Introduction

The platinum(II) complex cisplatin has become a salient drug in the therapy of solid tumors since Rosenberg and coworkers have discovered the anticancer activity of cisplatin in 1969 (Fig. 1) [1]. Cisplatin binds to DNA, i.e., its main cellular target, via coordination to the N-7 atom of purine bases such as guanine leading to toxic DNA cross-links [2,3]. Carboplatin and oxaliplatin feature additional anticancer drugs clinically approved in the USA and the EU (Fig. 1) [2–4]. However, drug resistance and toxic side-effects limit the application of these platinum complexes [3–6]. Thus, many new platinum complexes were designed such as Pt-complex-conjugates, *trans*-Pt complexes, Pt(IV) complexes, heteronuclear complexes and *N*-heterocyclic carbene complexes in order to overcome the eminent drawbacks of cisplatin, carboplatin and oxaliplatin [7–11].

MicroRNAs (miRNAs) feature another possibility to investigate the modes of platinum resistance and activity in order to design improved therapy options. About two thousand miRNAs featuring highly conserved non-coding RNAs of 22–23 nucleotides regulate circa one-third of all human genes including genes involved in significant cellular processes such as cell proliferation, cell differentiation and cell death [12,13]. MiRNAs have become valuable tools for the establishment of prognoses for cancer patients because of the characteristic miRNA expression patterns in tumor tissues [14–18]. In addition, certain miRNAs regulate the survival of drug-resistant cancer stem-like cells (CSCs) that are responsible for relapse [19,20]. MiRNAs are also involved in the regulation of metastasis formation, in particular, in the control of the epithelial-to-mesenchymal transition (EMT) of cancer cells [21,22].

In most cases, mature miRNAs bind to the 3'-untranslated region (3′UTR) of the target messenger RNAs (mRNAs) and, thus, inhibit the translation of these mRNAs [23]. One miRNA species is able to regulate various genes, and both tumor suppressor miRNAs and oncogenic miRNAs (oncomirs) are dysregulated in various human cancer types [24,25]. The detailed understanding of the modes of action of miRNAs with effects on cellular cancer-related processes is crucial for the development of improved anticancer therapies [26–28]. A recent review published in this journal before dealt with miRNA-modulating natural phenols and terpenoids and their effects on various tumors [29]. This review provides an overview of widely applied anticancer active platinum complexes (cisplatin,

Abbreviations: CBDCA, cyclobutane-1,1-dicarboxylate; DACH, 1,2-diaminocyclohexane; DDP, cisplatin; dTTP, deoxythymidine triphosphate; EGCG, (−)-epigallocatechin-3-gallate; EOX, epirubicin/oxaliplatin/xeloda; FOLFOX, folinate/5-FU/oxaliplatin; 5-FU, 5-fluorouracil; GC, gemcitabine/cisplatin, gastric cancer; LNA, locked nucleic acid; MVAC, methotrexate/vinblastine/adriamycin/cisplatin; XELOX, xeloda/oxaliplatin.

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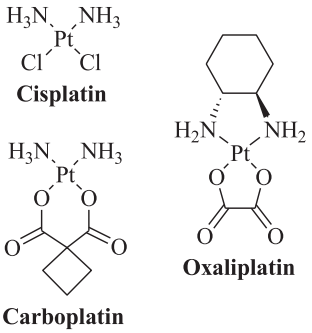

Fig. 1. Structures of the platinum(II) complexes cisplatin, carboplatin and oxaliplatin.

carboplatin, oxaliplatin) and their interactions with miRNAs.

2. Platinum complexes and their interactions with miRNAs

2.1. Cisplatin

Cisplatin, *cis*-(diammine)dichloridoplatinum(II), was the first platinum complex that was approved for anticancer therapy by the FDA in the USA in 1978 [30]. The chlorido ligands of the square-planar complex cisplatin can be replaced by *S*- and *N*-bio-nucleophiles of proteins and nucleic acids in the target cells and, in particular, the resulting DNA damage (DNA crosslinks, e.g., 1,2-intrastrand crosslinks) by cisplatin leads to apoptosis induction [2,3,30]. Cisplatin is widely applied against testicular cancer, non-small and small cell lung cancer, ovarian cancer, cervix carcinoma, prostate carcinoma, endometrial cancer, bladder cancer, melanoma, various sarcomas, and head-and-neck cancer [30]. It is given to the cancer patients as intravenous chloride infusions and the supplemented chloride salt prevents ligand exchange of cisplatin molecules in aqueous solutions [30]. Since the main mode of action of cisplatin is binding to DNA via guanine bases, the interactions of cisplatin with miRNAs, which represent short oligonucleotides, are of particular interest in order to get deeper insights into the modes of cisplatin action in cancer cells.

2.1.1. Cisplatin, miRNAs and ovarian cancer

Ovarian cancer solely affects women and features one of the main applications of cisplatin-based therapies and the microRNA profile of cisplatin-resistant ovarian cancer cells when compared with cisplatin-sensitive ovarian cancer cells was investigated [31]. In fact, five miRNAs (miRPlus-F1064, miR-300, miR-193b, miR-642, miR-1299) were up-regulated while six miRNAs (let-7c, miR-20b, miR-542-3p, miR-625, miRPlus-F1147, miRPlus-F1231) were downregulated in the resistant ovarian cell line A2780/CP70 when compared with the sensitive A2780 cells and was accompanied by significant influences on various signaling pathways (e.g., MAPK, TGF-β, Wnt, mTOR, Notch), apoptosis, actin cytoskeleton and proteasomal mechanisms [31]. Cisplatin-resistance of ovarian cancer cells was also induced by downregulation of the tumor suppressor let-7i [32]. Downregulated let-7i was associated with shorter PFS (progression free survival) in late-stage ovarian cancer patients [32]. In addition, suppression of miR-29 inhibited cisplatin-mediated apoptosis by induction of COL1A1 (collagen type I alpha I) in ovarian cancer cells [33]. MiR-30a sensitized ovarian cancer cells to cisplatin treatment by suppression of ETAR (endothelin-1/ETA receptor) and inhibition both of Akt signaling and of MAPK (mitogen-activated protein kinase) signaling [34]. The increased expression of miR-30c-2 sensitized cisplatin-resistant ovarian cancer cells via inhibition of the oncoprotein Bcl-9 [35]. The ABC-transporter ABCD2 was suppressed by miR-30d in ovarian cancer cells which was associated with enhanced apoptosis induction by cisplatin possibly via increased cisplatin accumulation in the cancer cells [36]. Suppressed miR-130a levels were observed from cisplatin-resistant ovarian cancer cells, and induced miR-130a expression downregulated XIAP (X-linked inhibitor of apoptosis) leading to cisplatin-sensitivity [37]. Another study of the miRNA profile of cisplatin-resistant ovarian cancer cells revealed lower levels of let-7e, miR-30c, miR-130a, and miR-335 in the resistant cancer cells [38]. In epithelial ovarian cancer, upregulated miR-136 augmented cisplatin-sensitivity significantly [39]. Further to this, the tumor suppressor miR-155 enhanced cisplatin-induced apoptosis in SKOV3 and A2780 ovarian cancer cells by inhibition of XIAP [40]. Both miR-152 and miR-185 were suppressed in cisplatin-resistant ovarian cancer cells and expression of miR-152 and miR-185 overcame cisplatin resistance via suppression of DNMT1 (DNA methyltransferase 1) [41]. EMT in EOC patients was correlated with reduced miR-186 expression and upregulated Twist1 transcription factor, while increased miR-186 expression was able to revert EMT and to increase cisplatin activity in ovarian cancer cells via suppression of Twist1 [42]. MiR-199a inhibited mTOR (mammalian target of rapamycin) expression and signaling in ovarian cancer cells leading cisplatin-sensitivity [43]. IGROV-1 ovarian cancer cells exhibited increased cisplatin activity due to induced expression of miR-302b and inhibition of HDAC4 (histone deacetylase 4) expression [44]. The tumor suppressor miR-449a inhibited Notch-1 expression associated with promoted cisplatin sensitivity in ovarian cancer cells [45]. Another tumor suppressor, miR-509-3p, blocked XIAP expression and increased cisplatin-mediated apoptosis induction in epithelial ovarian cancer cells [46]. MiR-519d features another XIAP inhibitor expressed in ovarian cancer cells that respond well to cisplatin treatment [47]. MiR-770-5p was shown to target ERCC2 (excision repair cross-complementation group 2) and, thus, blocked cisplatin resistance formation by ovarian cancer [48]. In addition, the expression of miR-873 blocked MDR1 (multidrug-resistance protein 1, Pgp) expression leading to improved cisplatin response by ovarian cancer cells and inhibition of multidrug resistance formation [49].

In contrast to that, inhibition of miR-9 sensitized ovarian cancer cells to cisplatin treatment [50]. Expression of the oncomir miR-21 led to cisplatin resistance of ovarian cancer cells via suppressed PDCD4 (programmed cell death protein 4) levels [51]. Its passenger strand, miR-21-3p, also increased cisplatin resistance in various ovarian cancer cell lines via suppression of NAV3 (neuron navigator 3) [52]. Interestingly, the natural isoquinoline alkaloid berberine suppressed miR-21 in SKOV3 ovarian cancer cells and augmented cisplatin activity in these cancer cells via induction of PDCD4 [53]. In platinum-resistant ovarian cancer patients, high levels of miR-27a were discovered which was associated with poor prognosis [54]. In addition, cisplatin-resistant ovarian cancer cells exhibited upregulated miR-31 expression leading to the suppression of KCNMA1 (potassium channel calcium activated large conductance subfamily M alpha, member 1) [55]. High expression of miR-93 blocked PTEN (phosphatase and tensin homolog) expression and inhibited cisplatin-induced apoptosis in cisplatin-resistant ovarian cancer cells via induction of Akt-signaling [56]. Further to this, the expression of miR-106a suppressed PDCD4 and induced cisplatin resistance in ovarian cancer [57]. Oncogenic miR-125b mediated cisplatin resistance in ovarian cancer cells via suppression of pro-apoptotic Bak1 [58]. Interestingly, another group has shown that expression of miR-130a and miR-374a reduced the activity of cisplatin in ovarian cancer cells accompanied by increased expression of the drug efflux pumps MDR1 and Pgp [59]. This is in contrast to the previous finding that miR-130a contributed to cisplatin-sensitivity via XIAP inhibition in ovarian cancer cells [37].