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.

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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,
cargoblatin, 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 pro-tosomal 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 1) 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]. In contrast to the previous miRNA expression downregulated XIAP (X-linked inhibitor of apoptosis) cisplatin-resistant ovarian cancer cells revealed lower contrast to the previous miRNA expression downregulated XIAP (X-linked inhibitor of apoptosis) cisplatin-resistant ovarian cancer cells, and induced miR-130a expression downregulated XIAP (X-linked inhibitor of apoptosis) leading to cisplatin-sensitivity [37]. 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]. 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].
Taxol-resistant A2780/Taxol ovarian cancer cells also showed reduced sensitivity to cisplatin via upregulated miR-130b which was correlated with increased expression of MDR1, Pgp (P-glycoprotein) and GST-π (glutathione S-transferase) [60]. In addition, miR-141 expression was responsible for cisplatin resistance in ovarian cancer cells via downregulation of KEAP1 (Kelch-like ECH-associated protein 1) [61]. Omental metastases of epithelial ovarian cancer cells via downregulation of KEAP1 (Kelch-like ECH-associated protein 1) [61]. Omental metastases of epithelial ovarian cancer cells via downregulation of KEAP1 (Kelch-like ECH-associated protein 1) [61]. Omental metastases of epithelial ovarian cancer cells via downregulation of KEAP1 (Kelch-like ECH-associated protein 1) [61]. Omental metastases of epithelial ovarian cancer cells via downregulation of KEAP1 (Kelch-like ECH-associated protein 1) [61]. Omental metastases of epithelial ovarian cancer cells via downregulation of KEAP1 (Kelch-like ECH-associated protein 1) [61]. Omental metastases of epithelial ovarian cancer cells via downregulation of KEAP1 (Kelch-like ECH-associated protein 1) [61].

Onconegic miR-214 suppressed PTEN expression and activated Akt signaling accompanied by cisplatin resistance in ovarian cancer cells [63]. Cisplatin resistance of ovarian papillary serous carcinoma was associated with expression of miR-224-5p leading to inhibition of PRKCD (protein kinase C δ) [64]. The expression of miR-376c inhibited ALK7 (activin receptor-like kinase 7) expression in epithelial ovarian cancer cells leading to cisplatin resistance [65]. Another PTEN inhibitor of ovarian cancer cells is featured by miR-630, and suppression of miR-630 increased cisplatin activity in epithelial ovarian carcinoma cells [66]. Recently, it was shown that oncogenic miR-630 levels were increased after cisplatin treatment via induction of the transcription factor E2F1 and of the miRNA-processing Drosha protein [67]. A list of miRNAs involved in cisplatin-resistance and -sensitivity of ovarian cancers is given in Table 1.

The processing of miRNAs into their mature form strongly depends on the enzyme Dicer, and suppression of Dicer induced chemoresistance and invasive cancer forms [68]. In particular, knockdown of Dicer reduced the activity of cisplatin in A2780 ovarian cancer cells [68]. More recently, inhibition of the RNA-binding protein DGC8 (digeorge critical region 8), which processes primary miRNA (pri-miRNA) into precursor miRNA (pre-miRNA) together with the RNase III Drosha in the nucleus, enhanced the activity of cisplatin via downregulation of miR-27b [69].

### Table 1

**MicroRNA tumor suppressors and oncogenes correlated with cisplatin activity in ovarian cancers.**

| Tumor suppressors | Oncogenes |
|-------------------|------------|
| let-7c, let-7i, miR-20b, miR-29, miR-30a, miR-30c, miR-30c-2, miR-30d, miR-130a(1), miR-136, miR-152, miR-155, miR-185, miR-186, miR-199a, miR-302b, miR-335, miR-44a, miR-509-3p, miR-519d, miR-542-3p, miR-625, miR-770-5p, miR-873, miRPlus-F1147, miRPlus-F1231 | miR-9, miR-21, miR-21-3p, miR-27a, miR-27b, miR-31, miR-93, miR-106a, miR-125b, miR-130a(1), miR-130b, miR-141, miR-146a, miR-150, miR-193b, miR-214, miR-224-5p, miR-300, miR-374a, miR-376c, miR-630, miR-642, miR-1299, miRPlus-F1064 |

### 2.1.2. Cisplatin, miRNAs and lung cancer

Non-smokers are almost exclusively affected by non-small cell lung cancer (NSCLC), while smoking patients usually suffer from small-cell lung cancer (SCLC), and over one million people (both men and women) die of lung cancer worldwide every year [70,71]. Platinum complexes such as cisplatin and carboplatin have become crucial parts of chemotherapeutic treatments both of small-cell and of non-small-cell lung cancers, and have improved the survival of lung cancer patients significantly when administered in combination with other anticancer drugs such as gemcitabine, etoposide, vinorelbine or paclitaxel [70,71]. The role of miRNAs for the anti-lung cancer activity of cisplatin was thoroughly investigated, and the tumor suppressor miR-15a-3p enhanced the activity of cisplatin in NSCLC cells via suppression of the anti-apoptotic Bcl-2 protein [72]. Expression of let-7c sensitized cisplatin-resistant A549/DDP NSCLC cells to cisplatin treatment via suppression of the ABC-transporter ABC2C2 and Bcl-xL [73]. Let-7i was suppressed in cisplatin-resistant A549/DDP NSCLC cells as well as the long non-coding RNA (IncRNA) AK126698 which lead to activation of the Wnt[beta]-catenin signaling pathway [74]. The expression of miR-17 family miRNAs (miR-17, miR-20a, miR-20b) in A549 NSCLC cells blocked cisplatin resistance by inhibition of the TGF-beta (transforming growth factor) signaling pathway and repression of TGF-beta receptor 2 (TGF-beta2) [75]. Suppression of miR-17 and miR-23a families in NSCLC was correlated with cisplatin resistance via upregulation of CDKNA1 (cyclin-dependent kinase inhibitor 1A) and of the double-strand break repair protein RAD21 leading to efficient DNA repair [76]. Downregulation of miR-26a was associated with resistance to cisplatin treatment in NSCLC cells, and restored miR-26a expression increased cisplatin activity via inhibition of HMGGA2/E2F1/Akt signaling pathway and suppression of Bcl-2 [77]. Reduced levels of miR-29b were found in NSCLC tissues and restored miR-29b expression sensitized NSCLC cells to cisplatin via downregulation of CDK6 (cyclin-dependent kinase 6), DNM3TB3 and Mcl-1 (myeloid cell leukemia sequence 1) expression [78]. Restoration of miR-34a expression in lung tumors led to improved survival of cisplatin-treated KP mice bearing lung tumors [79]. MiR-34a-mediated suppression of PEBP4 increased cisplatin activity in resistant lung cancer cells [80]. In addition, miR-34a sensitized cisplatin-resistant lung cancer cells independent of their p53 activity state and the combination of miR-34a expression with cisplatin treatment seemed feasible [81]. Drug-resistant A549/DDP NSCLC cells showed reduced levels of miR-155a/b associated with cisplatin resistance via upregulation of Mcl-1 [82]. Increased levels of miR-138 were accompanied by reduced ERCC1 expression leading to enhanced cisplatin activity in NSCLC cells [83]. The tumor suppressor miR-148b sensitized drug-resistant NSCLC cells to cisplatin via inhibition of DNMT1 [84]. Further to this, miR-181b expression inhibited TGF-beta1/Smad signaling leading to cisplatin sensitivity of NSCLC cells [85]. MiR-181b also downregulated anti-apoptotic Bcl-2 and Bcl-xL associated with increased cisplatin activity in drug-resistant A549 NSCLC cells [86]. Expression of let-7c and miR-200b reverted EMT in lung cancer cells and re-sensitized cancer cells to treatment with erlotinib and cisplatin [87]. The miR-200bc/429 cluster was downregulated in cisplatin-resistant A549/DDP NSCLC cells associated with upregulated anti-apoptotic Bcl-2 and XIAP, and expression of miR200bc/429 led to increased apoptosis induction by cisplatin [88]. In SCLC cells, suppressed miR-200b expression was observed leading to cisplatin resistance via ZEB2 (zinc-finger E-box-binding homeobox 1) [89]. In addition, expression of miR-200c restored cisplatin activity in H1266 NSCLC cells via upregulation of E-cadherin and suppression of N-cadherin [90]. Cisplatin-mediated tumor cell growth inhibition and apoptosis induction was promoted by expression of miR-216a in NSCLC cells leading to suppression of eIF4B (eukaryotic initiation factor 4B) and ZEB1 [91]. The tumor suppressor miR-217 sensitized lung cancer cells to cisplatin treatment via KRAS ( Kirsten-rat sarcoma) downregulation [92]. The expression of miR-375 was reduced in ERCC1-positive NSCLC tumors associated with reduced cisplatin activity [93]. In addition, upregulation of miR-378 sensitized cisplatin-resistant A549/DDP and Anip973/DDP lung adenocarcinoma cells to cisplatin treatment via suppression of secreted clusterin (slCu) [94]. Suppression of Akt signaling and Bcl-2 was observed from A549 lung cancer cells expressing miR-451 which led to increased sensitivity to cisplatin treatment [95]. NSCLC cells expressing miR-
495 exhibited higher cisplatin activity than cells with suppressed mir-495, and miR-495 blocked the expression of the copper transporter ATPase A7P, which is involved in multidrug resistance [96]. Downregulated miR-497 was observed from cisplatin-resistant A549/DDP NSCLC cells associated with induction of anti-apoptotic Bcl-2 protein expression [97]. Reduced expression of mir-503 was also detected in A549/DDP NSCLC cells, and induced mir-503 expression enhanced cisplatin activity via Bcl-2 suppression [98]. The tumor suppressor mir-509-3-5p sensitized A549 NSCLC cells to cisplatin treatment via PKL1 (polo-like kinase 1) suppression and cell cycle arrest [99]. MiR-630 suppressed CDC7 (cell division cycle 7) kinase and augmented cisplatin activity in A549 cells [100]. NSCLC patients expressing significant levels of miR-638 revealed longer survival and better response to cisplatin chemotherapy [101].

MiR-15b induced cisplatin resistance of lung cancer cells by downregulation of PEBP4 (phosphatidylethanolamine-binding protein 4) [102]. The oncogenic miR-21 enhanced cisplatin resistance in A549 lung cancer cells by downregulation of PTEN and induction of anti-apoptotic Bcl-2, and miR-21 expression can be applied as a marker for cisplatin response and survival prognoses in NSCLC patients [103]. Suppression of oncogenic miR-25 leading to CDC24 downregulation augmented cisplatin activity in A549 NSCLC cells [104]. MiR-25 was also overexpressed in SCLC cells associated with cisplatin resistance and expression of CDK2 (cyclin-dependent kinase 2) and cyclin E2 [105]. Single nucleotide polymorphism (SNP) in the pre-miR-27a led to increased levels of the oncogene miR-27a associated with poorer response to cisplatin in Chinese NSCLC patients harbouring this genetic polymorphism [106]. Expression of miR-31 blocked cisplatin-mediated apoptosis in NSCLC cells via inhibition of the ABCB9 transporter [107]. Inhibition of the PTEN repressor mir-92b sensitized resistant A549/DDP lung cancer cells to cisplatin [108]. Cisplatin treatment of A549 NSCLC cells increased p53 levels and reduced Bcl-2 and miR-98 expression, a negative regulator of p53, and upregulated miR-98 suppressed p53, which is a crucial protein for cisplatin-induced apoptosis [109]. However, there's another report about miR-98 which described cisplatin sensitivity in miR-98 expressing A549 cells associated with increased HMGAA2 levels and lowered Bcl-2 levels [110]. (−)-Epigallocatechin-3-gallate (EGCG), the major natural catechin of the tea plant Camellia sinensis, suppressed oncogenic miR-98-5p leading to induction of p53 expression and increased cisplatin activity in NSCLC cells [111]. MiR-100 was upregulated in cisplatin-resistant SCLC cells leading to suppression of HOXA1 (homeobox A1) [112]. Both miR-106 and miR-150 functioned as oncogenes in A549 lung cancer cells, and inhibition of miR-106 and miR-150 by antisense oligonucleotides enhanced the activity of cisplatin in these cells [113]. Increased miR-106a expression led to cisplatin resistance in A549 NSCLC cells via suppression of the ABC transporter ABCA1, which is a transporter involved in cisplatin uptake [114]. Another oncormir, miR-128-2, suppressed the p21-repressor E2F5 in NSCLC cells leading to inhibition of apoptosis induction by cisplatin [115]. Expression of miR-145 decreased cisplatin activity in NSCLC cells by suppression of CDK6 [116]. In addition, suppressed miR-155 led to decreased Bax levels and increased apoptosis induction by cisplatin in A549 NSCLC cells [117]. Oncogenic miR-186* was suppressed by treatment with curcumain, a natural phenolic derivative from the roots of Curcuma longa (turmeric), and reduced miR-186* levels were associated with increased cisplatin activity in resistant A549/DDP NSCLC cells [118]. Cisplatin-resistant A549/DDP cells also showed increased levels of miR-192, and inhibition of miR-192 sensitized these lung cancer cells to cisplatin via suppression of Bcl-2 and upregulation of Bax [119]. MiR-205 features another PTEN repressor and miR-205 expression was associated with cisplatin resistance in NSCLC cells [120]. Upregulated miR-224 contributed to cisplatin resistance of lung adenocarcinoma cells via p21(1WF/A/CIP1) suppression [121]. The miR-499 rs3746444T > C polymorphism was identified as a marker for bad prognosis and cisplatin resistance in lung cancer patients [122]. A list of miRNAs involved in cisplatin-resistance and sensitivity of lung cancers is given in Table 2.

### 2.1.3. Cisplatin, miRNAs and breast cancer

Among female cancer patients, breast cancer diseases represent the major cause of death though mortality rates were reduced by 36% since 1989 [123]. The efficacy of cisplatin treatment in breast cancer patients was correlated with certain miRNA expression profiles [123]. Cisplatin-resistance of breast cancer cells was induced by downregulation of the tumor suppressor let-7i [32]. MiR-7 and miR-345 suppressed the multidrug resistance associated transporter MRPI in cisplatin-resistant MCF-7/DDP breast cancer cells [124]. In addition, miRNAs of the miR-200 family were downregulated in cisplatin-resistant MCF-7/DDP cells [124]. MiR-128 induced apoptosis in a p53-independent way and increased cisplatin activity in MCF-7 breast cancer cells [125]. BRCA1 (breast cancer 1) protein expression was induced in cisplatin-resistant MCF-7/DDP breast cancer cells because of suppression of miR-218 and restoration of miR-218 expression sensitized these cells to cisplatin again [126]. The expression of miR-638 was downregulated in breast cancer cells and induced miR-638 expression sensitized triple-negative breast cancer cells to cisplatin treatment [127].

Concerning oncomirs, TGF-β-induced miR-21 expression contributed to cisplatin resistance in breast cancer cells [128]. In line with this finding, transfection of MCF-7 breast cancer cells with an anti-miR-21 oligonucleotide increased cisplatin activity in these cells [129]. In addition, cisplatin-resistant MCF-7/DDP cells showed increased levels of oncogenic miR-10a, miR-146a, miR-221 and miR-222, which control the expression of BRCA1 (breast cancer 1), p27 and Erkz (estrogen receptor z) [124]. MiR-221 knockdown also induced pro-apoptotic Bim expression leading to enhanced cisplatin activity in breast cancer cells [130]. Suppression of miR-203 expression by anti-miR-203 increased cisplatin activity in MCF-7 breast cancer cells by induction of SOCS3 (suppressor of cytokine signaling 3) [131]. Overexpression of miR-569 contributed to aggressiveness of breast tumors including increased cancer cell survival and proliferation by downregulation of TP53INP1, and suppression of miR-569 augmented cisplatin activity in breast cancers [132]. A list of miRNAs involved in cisplatin-resistance and sensitivity of breast cancers is given in Table 3.

### Table 2

MicroRNA tumor suppressors and oncogenes correlated with cisplatin activity in lung cancers.

| Tumor suppressors | Oncogenes |
|-------------------|-----------|
| let-7c, let-7i, miR-15a-3p, miR-17, miR-20a, miR-20b, miR-26a, miR-29b, miR-34a, miR-98(1), miR-135b, miR-148b, miR-181b, miR-200b, miR-200c, miR-216a, miR-375, miR-378, miR-429, miR-451, miR-495, miR-497, miR-503, miR-509-3-5p, miR-630, miR-638 | miR-15b, miR-21, miR-25, miR-27a, miR-31, miR-92b, miR-98(4), miR-98-5p, miR-100, miR-106a, miR-126-2, miR-145, miR-150, miR-155, miR-186*, miR-192, miR-205, miR-224, miR-499 rs3746444T > C |

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2.1.4. Cisplatin, miRNAs, head-and-neck cancers and esophageal cancers

Head-and-neck cancers are mostly squamous cell carcinomas that can affect oral (tongue), nasopharyngeal, and laryngeal parts of the cancer patient, and head-and-neck squamous cell carcinoma (HNSCC) is the 6th most common cancer worldwide [133]. HNSCC is particularly prevalent in India where 30% of all cancers are HNSCC [134,135]. Esophageal cancers represent the 8th most common cancer worldwide and squamous cell carcinomas (ESCC) are predominant among esophageal cancer cases as well [136]. Cisplatin-based therapies are applied for head-and-neck and esophageal cancers though the response rate in the latter case is only moderate (19–40%) [136–138]. Certain miRNAs can play a role concerning the response of head-and-neck and esophageal cancers to cisplatin. In HNSCC cells, cisplatin treatment led to suppression of miR-181a, miR-374a, and miR-519a, while miR-630 expression was induced [139]. Inhibition of miR-630 led to increased tumor cell survival, while inhibition of miR-181a, miR-374a and miR-519a reduced cell survival [139]. Nasopharyngeal carcinoma (NPC), which is prevalent in South China and Southeast Asia, is induced by the Epstein-Barr virus (EBV) and EBV-encoded BART Cluster 1 miRNAs reduced cisplatin activity via LMP1 suppression [140]. Induction of the tumor suppressor miR-16 after CDK4 knockdown in NPC cells was associated with enhanced cisplatin activity [141]. NPC cells with EBV-encoded LMP1 (latent membrane protein 1) induced miR-21 expression leading to inhibition of cisplatin-induced apoptosis via downregulation of PDCD4 and Fas-L [142]. MiR-21 also reduced cisplatin activity in tongue squamous cell carcinomas via suppression of PDCD4 [143]. Downregulation of miR-30a in HNSCC enhanced cisplatin activity and blocked cell motility via inhibition of Bcl-2 [144]. In addition, expression of miR-98 in HNSCC cells enhanced cisplatin resistance by suppression of HMGAA2 (high mobility group A2) [145]. Upregulation of miR-125a and miR-125b in cisplatin-treated NPC cells silenced cisplatin-mediated apoptosis induction by suppression of p53 [146]. Induction of miR-101-3p in laryngeal cancer (LC) cells augmented cisplatin resistance because miR-101-3p inhibited RIPK1 (receptor-interacting serine/threonine kinase 1) expression [147]. Another oncormi, miR-222, was inhibited by antisense-miR-222 in oral squamous cell carcinoma (OSCC) cells leading to PUMA (p53 upregulated modulator of apoptosis) expression and increased cisplatin activity [148]. In addition, expression of miR-134 in OSCC cells increased cisplatin activity [149]. Tongue squamous cell carcinoma (TSCC) revealed high miR-24 expression associated with cisplatin resistance and PTEN suppression [150]. Further to this, TSCC tumors with suppressed miR-200c and miR-15b expression exhibited resistance to cisplatin-based chemotherapy and poorer prognosis of TSCC patients [151]. In contrast to that, TSCC cells with increased miR-23a and miR-214 expression levels were cisplatin-resistant because of suppression of TOP2B (DNA topoisomerase II beta) [152]. Cisplatin-resistant LC cells (Hep-2/v cells) exhibited upregulated miR-210 and miR-923 expression while miR-93 was suppressed in the multidrug-resistant cancer cells, this miRNA profile of resistant LC cells was accompanied by suppression of serine protease HTRA1 and NUPR1 (nuclear protein 1), and induction of RGS10 (regulator of G-protein signaling 10) expression [153].

Esophageal squamous cell carcinoma (ESCC) cells with reduced expression of let-7b and let-7c showed cisplatin resistance and restored let-7b/c expression in ESCC cells sensitized these cells to cisplatin treatment via downregulation of IL-6/STAT-3 (interleukin 6/signal transducer and activator of transcription 2) signaling [154]. Induced expression of let-7g and let-7i in esophageal cancer cells suppressed ABCC10 expression leading to increased cisplatin activity [155]. Patients suffering from ESCC or EAC (esophagogastric adenocarcinoma), most of them received cisplatin-based chemotherapies, with increased miR-21 levels exhibited shorter survival times [156]. In addition, ESCC cells with suppressed miR-27a (via antagonir miR-27a transfection) showed increased cisplatin activity because of Bcl-2 inhibition and Bax induction [157]. Pathologic complete response (pCR) in patients suffering from esophageal adenocarcinoma who received chemoradiation including 5-FU (5-fluorouracil) and platinum (cisplatin or oxaliplatin) therapy was correlated with reduced expression of miR-99b, miR-145*, miR-451, and miR-505* [158]. The proton pump inhibitor esomeprazole sensitized esophageal cancer cells (both ESCC and EAC) to cisplatin treatment and revealed increased expression of miR-141 and miR-200b as well as downregulated miR-376a levels [159]. However, miR-141 was also described as an oncomir highly expressed in cisplatin-resistant ESCC cells leading to YAP1 (yes-associated protein 1) suppression [160]. EAC cells (SK-GT-4) expressing miR-145 exhibited distinct cisplatin resistance and promoted cancer cell invasion [161]. MiRNA polymorphisms also play a role for cisplatin resistance and the TT genotypes of miR-196a2 rs11614913 and miR-125a rs12976445 were associated with reduced survival of ESCC patients receiving platinum-based therapy (cisplatin or oxaliplatin) [162]. Cisplatin treatment of ESCC and EAC cells exhibited changes in miRNA expression associated with cell survival, three miRNAs (miR-342-3p, miR-425, miR-320a) were upregulated by cisplatin in ESCC cells, while two miRNAs (miR-548d-5p, miR-455-3p) were suppressed in EAC cells [163]. In addition, increased expression of miR-200c was correlated with cisplatin resistance in esophageal cancer patients via induction of Akt signaling and inhibition of P22A (protein phosphatase 2A) [164]. MiR-330-3p features another oncomir that suppressed PDCD4 in ESCC cells accompanied by inhibition of cisplatin-mediated apoptosis [165]. Expression of the tumor suppressor miR-507 augmented cisplatin activity in ESCC tumors via suppression of NRF2 (NF-E2-related factor 2) [166]. Another study of the miRNA profile of cisplatin-resistant ESCC and EAC cells revealed eleven dysregulated miRNAs in EAC cells (miR-191-5p and miR-638 were upregulated, and let-7e-5p, miR-31-5p, miR-125-5p, miR-181a-5p, miR-181b-5p, miR-200a-3p, miR-200b-3p, miR-200b-5p, and miR-455-3p were suppressed) and one upregulated miRNA (miR-130-3p) in EAC cells [167]. A list of miRNAs involved in cisplatin-resistance and -sensitivity of head-and-neck cancers and esophageal cancers is given in Table 4.

2.1.5. Cisplatin, miRNAs and gastric cancers

Gastric cancer (GC) belongs to the most common cancers worldwide (in particular, in Asia) and features the 2nd most cause of cancer deaths [168]. Dysregulation of tumor suppressors and oncogenes was observed from gastric cancers, including the modulation of miRNA expression in the course of carcinogenesis and chemotherapy [169,170]. Advanced gastric cancer diseases are commonly treated with cisplatin, however, increased toxicity and emergence of resistance represent significant drawbacks of this
A strong influence of miRNAs on cisplatin activity in gastric cancers was assumed. Expression of oncogenic miR-20a in gastric cancers activated NF-κB (nuclear factor κB) signaling via repression of NFKBIB (κB) leading to cisplatin resistance of GC cells [172]. In addition, miR-20a induced cisplatin resistance in GC cells by downregulation of EGR2 (early growth response 2) [173]. Oncogenic miR-21 suppressed PTEN and induced Akt signaling leading to cisplatin resistance of GC cells [174]. Cisplatin treatment induced the expression of miR-29c and suppressed the oncogenic targets of miR-29c (catenin-β and Rho signaling), which was associated with reduced metastasis formation and lower relapse rates in gastric cancer patients [175]. Expression of miR-30a increased cisplatin activity in GC cells via inhibition of Snail and vimentin and reversal of EMT [176]. In addition, expression of miR-101 enhanced cisplatin activity in cisplatin-resistant SGC7901/DDP cells by inhibition of VEGF-C (vascular endothelial growth factor C) expression [177]. Sensitivity of GC cells to cisplatin was promoted by downregulation of oncogenic miR-141 and induction of the miR-141 target KEAP1, and Helicobacter pylori bacteria were able to suppress miR-141 in GC cells and to augment cisplatin activity [178]. However, another study on miR-141 and the long-coding RNA (lncRNA) H19 showed that miR-141 expression downregulated the oncogenic lncRNA H19 leading to proliferation inhibition and increased cisplatin activity [179]. Expression of the tumor suppressor miR-200c promoted cisplatin activity in resistant SGC-7901/MMR cells via induced expression of E-cadherin and pro-apoptotic Bax as well as downregulation of anti-apoptotic Bcl-2 [180]. In addition, RhoE was identified as a target of miR-200c and suppression of RhoE sensitized cisplatin-resistant GC cells to cisplatin [181]. Expression of miR-218 in GC cells (SCC7901) enhanced the sensitivity of these cancer cells to cisplatin treatment, and miR-218 was induced in advanced GC patients after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy [182]. In contrast to that, cisplatin-resistant GC cells exhibited increased miR-223 expression, which contributed to drug resistance by downregulation of FBXW7 (F-box and WD repeat domain containing 7) [183]. GC tissues and cells infected by H. pylori showed upregulated miR-223 expression, which may play a role for the emergence of cisplatin resistance in gastric cancers [183]. This is in contrast to the observation that H. pylori suppressed miR-141 expression in GC cells associated with increased cisplatin activity [178]. In addition, overexpression of miR-362 in GC cells (BGC-823, SCC-7901) induced cisplatin-mediated apoptosis induction via activation of NF-κB [184]. Downregulation of miR-375 contributed to cisplatin resistance of GC cells (SCC7901/DDP) because of induction of the receptor tyrosine kinase ERBB2 and activation of Akt signaling [185]. Activation of NF-κB signaling induced the expression of miR-425 leading to PTEN suppression and cisplatin resistance [186]. The tumor suppressor miR-449a inhibited Bcl-2 and cyclin D1 expression in GC cells and, thus, enhanced cisplatin-induced apoptosis [187]. In addition, the tumor suppressor miR-503 inhibited Bcl-2 and IGF1R (insulin-like growth factor receptor 1) expression associated with increased apoptosis induction by cisplatin [188]. Upregulation of miR-765 sensitized BGC-823/DDP cells to cisplatin via inhibition of CIAPIN1 (cytokine-induced apoptosis inhibitor 1) expression [189]. MiR-1271 expression also sensitized GC cells to cisplatin treatment via inhibition of IGF1R, IRS1, mTOR and Bcl-2 expression [190]. Samples of gastric cancer patients exhibited upregulated expression of six miRNAs (let-7g, miR-1, miR-16, miR-34, miR-181, miR-342) which were associated with chemosensitivity to cisplatin treatment [191]. Further to this, miR-181a blocked autophagy in GC cells and increased cisplatin activity in SCC7901/DDP cells [192]. A list of miRNAs involved in cisplatin activity in gastric cancers is given in Table 5.

| miRNAs involved in cisplatin-resistance and –sensitivity in head-and-neck cancers and esophageal cancers. |
|---|
| Sensitivity | Resistance |
| miR-15b, miR-16, miR-93, miR-134, miR-200c, miR-630 | BART Cluster 1 miRNAs (EBV), miR-21, miR-23a, miR-24, miR-30a, miR-98, miR-101-3p, miR-125a, miR-125b, miR-181a, miR-210, miR-214, miR-222, miR-374a, miR-519a, miR-923 |
| let-7b, let-7c, let-7e-5p, let-7g, let-7i, miR-31-5p, miR-125-5p, miR-141(1), miR-181a-5p, miR-181b-5p, miR-200a-3p, miR-200b-5p, miR-200b-3p, miR-455-3p, miR-507, miR-548d-5p | miR-218, miR-79, miR-99b, miR-125a rs129796445, miR-130-3p, miR-141(1), miR-145, miR-145*, miR-191-5p, miR-195a2 rs1614913, miR-200c, miR-320a, miR-330-3p, miR-342-3p, miR-376a, miR-425, miR-451, miR-505*, miR-638 |

Table 5 MicroRNA tumor suppressors and onco genes correlated with cisplatin activity in gastric cancers.

| Tumor suppressors | Oncogenes |
|---|---|
| let-7g, miR-1, miR-16, miR-29c, miR-30a, miR-34, miR-141(1), miR-181, miR-181a, miR-200c, miR-218, miR-342, miR-375, miR-449a, miR-503, miR-1271 | miR-20a, miR-21, miR-141(1), miR-223, miR-362, miR-425 |

2.1.6. Cisplatin, miRNAs, hepatomas and renal cancers

Hepatocellular carcinoma (HCC) represents the 5th most common cancer worldwide and the 3rd most fatal cancer disease (more than 600,000 deaths per year) [193]. Renal cell carcinoma (RCC) is the most common kidney cancer leading to more than 13,000 deaths per year in the USA [194]. The activity of cisplatin against both cancer types was investigated and certain miRNAs played crucial roles for the performance of cisplatin. HCC patients who did not respond to cisplatin-based chemotherapy exhibited twelve upregulated miRNAs (miR-10a-1, miR-23a-1, miR-24, miR-26a, miR-27a, miR-30c, miR-30e, miR-106b, miR-133b, miR-199a, miR-199-3p, miR-200b) [195]. In addition, the regulation of ten miRNAs was correlated with patient survival and cisplatin activity, i.e., suppression of miR-602-2 and upregulation of nine miRNAs (let-7g-2, miR-21-2, miR-31-3, miR-98-1, miR-107-1, miR-181a-2, miR-210-1, miR-491-1, miR-664-1) were associated with better survival rates in HCC patients who received cisplatin treatment [195]. Expression of miR-27b enhanced cisplatin activity in HCC cells (HepG2) by p53 activation and inhibition of CYP1B1 (cytochrome P450 1B1) expression [196]. In contrast to that, the expression of oncogenic miR-1180 activated NF-κB signaling in HCC cells leading to cisplatin resistance [197]. Cisplatin-treated HCC cells showed altered miRNA expressions (upregulated miR-34a, miR-99a and miR-338-3p expression) which may contribute to growth inhibition and apoptosis induction by cisplatin [198]. In addition, expression of miR-133a and miR-326 downregulated the anti-apoptotic Bcl-xL protein which was associated with increased
cisplatin activity in HCC cells [199]. MiR-182 levels are increased in HCC patients receiving cisplatin-based chemotherapy and it was shown that miR-182 increased cisplatin resistance in HCC cells by suppression of TP53INP1 (tumor protein 53-induced nuclear protein 1) expression [200].

In renal cell carcinoma cells (RCC), levels of PTENP1 (a pseudogene of PTEN) were low and suppressed by oncogenic miR-21. Increased expression of PTENP1 was accompanied by increased cisplatin activity in RCC cells [201]. Like in HCC cells, p53 activation and CYP1B1 suppression were observed from RCC cells expressing miR-27b, which was associated with augmented cisplatin activity [196]. A list of miRNAs involved in cisplatin activity in hepatomas and renal cancers is given in Table 6.

### 2.1.7. Cisplatin, miRNAs, bladder cancer and colon cancer

Bladder cancer is the fourth most common cancer among men of the West, and standard chemotherapy includes cisplatin in combination with methotrexate, vinblastine, and doxorubicin (MVAC) or in combination with gemcitabine (GC) [202]. However, toxicity and drug resistance feature severe drawbacks of cisplatin therapy, which is in parts regulated by miRNAs. Bladder cancer cells that responded well to cisplatin treatment showed reduced levels of miR-138 and increased expression of miR-27a and miR-642 [202]. Restored miR-27a expression in cisplatin-resistance bladder cancer cells led to increased cisplatin activity by suppression of the cystine/glutamate exchanger SLC7A11 [203]. Cisplatin-induced expression of miR-34a in bladder cancer cells inhibited CD44 expression and potentiated cisplatin activity by suppression of the cell-cycle checkpoint protein RAD1 [204]. In addition, expression of miR-101 sensitized bladder cancer cells to cisplatin treatment by suppression of COX-2 (cyclooxygenase-2) [205]. MiR-1182 also sensitized bladder cancer cells to cisplatin via inhibition of hedgehog signaling and suppression of Gli3 [206]. In contrast to that, expression of miR-181a led to cisplatin resistance in CC cells by inhibition of pro-apoptotic PRKCD (protein kinase C delta) [218]. Further to this, inhibition of miR-199a by anti-miR-199a oligonucleotides augmented cisplatin activity in CC cells [219]. MiR-93 and miR-106b contributed to cisplatin resistance in CC cells by targeting the cell-cycle checkpoint protein RAD1 [220].

Prostate cancer (PCa) is the second most cause of death of male cancer patients in the West [133]. PCa cells expressing miR-29b increased apoptosis induction by cisplatin by suppression of Akt3 and DNMT3b [221]. In addition, suppression of miR-31 and miR-205 led to cisplatin resistance by upregulation of anti-apoptotic Bcl-w and E2F6 [222]. Inhibition of autophagy via suppression of lysosome-associated proteins RAB27A (a Ras-related protein) and LAMP3 (lysosomal associated membrane protein 3) by miR-205 in castration-resistant PCa cells was accompanied by enhanced cisplatin sensitivity in these cancer cells [223]. In contrast to that, expression of oncogenic miR-125b mediated cisplatin resistance by downregulation of p53, Bak1 and PUMA [224]. A list of miRNAs involved in cisplatin activity in cervical and prostate cancers is given in Table 8.

### 2.1.8. Cisplatin, miRNAs, cervical cancer and prostate cancer

Cervical cancer (CC) is one of the most common female cancers with high mortality rates (ranked 2nd among female cancers) [211]. Globally, there are ca. half a million new cases and ca. 230,000 women die of this cancer per year. Most cervical cancer patients suffer from squamous cell carcinomas (ca. 80%) while a minor group is affected by adenocarcinomas (5–20%) [212]. Cisplatin is applied in neoadjuvant chemotherapy of cervical cancer and this platinum complex increased miR-34a and miR-605 expression levels as well as p53 expression in cervical cancer samples from cancer patients [213]. HeLa CC cells, which expressed miR-30a, increased cisplatin-mediated apoptosis via suppression of Beclin-1 and inhibition of autophagy [214]. In addition, expression of miR-125a sensitized resistant CC cells to cisplatin by suppression of STAT-3 [215]. Induction of miR-124 and miR-502b suppressed Eps8 and potentiated cisplatin activity in HeLa CC cells [216]. MiR-506 also sensitized CC cells to cisplatin via inhibition of hedgehog signaling and suppression of Gli3 [217]. In contrast to that, expression of miR-181a led to cisplatin resistance in CC cells by inhibition of pro-apoptotic PRKCD (protein kinase C delta) [218]. Further to this, inhibition of miR-199a by anti-miR-199a oligonucleotides augmented cisplatin activity in CC cells [219]. MiR-93 and miR-106b contributed to cisplatin resistance in CC cells by targeting the cell-cycle checkpoint protein RAD1 [220].

### 2.1.9. Cisplatin, miRNAs and miscellaneous cancer diseases

Testicular germ cell tumors (TGCT) are the most common solid tumors among young men and the survival rate of TGCT patients has improved much since the approval of cisplatin in the late 1970’s [30]. Nevertheless, the influence of a few miRNAs on cisplatin activity in TGCT was investigated and the expression of miR-302a

### Table 6

| Micro-RNAs involved in cisplatin-resistance and –sensitivity in hepatomas and renal cancers. |
|---------------------------------------------|
| **Sensitivity** | **Resistance** |
| Hepatoma | miR-27b, miR-34a, miR-101, miR-642, miR-1182, miR-138, miR-150 |
| Renal cancer | miR-10a-1, miR-23a-1, miR-24, miR-26a, miR-27a, miR-30c, miR-30e, miR-106b, miR-133b, miR-182, miR-199a, miR-199-3p, miR-200b, miR-602-2, miR-1180, miR-21 |

### Table 7

| MicroRNA tumor suppressors and oncogenes correlated with cisplatin activity in bladder cancers and colon cancers. |
|---------------------------------------------|
| **Tumor suppressors** | **Onco genes** |
| Bladder cancer | miR-27a, miR-34a, miR-101, miR-642, miR-1182 |
| Colon cancer | miR-128, miR-203, miR-497 |
increased cisplatin activity in TGCT cells (NT2) via suppression of p21 [225]. In addition, NT2 cells expressing miR-383 exhibited suppressed PNOTUS (a subunit of protein phosphatase 1) and histone H2AX, which was associated with augmented cisplatin activity [226].

Endometrial cancer (EC) represents a female malignancy with poor prognosis. Expression of miR-134 in human EC stem cells was downregulated leading to reduced cisplatin activity, while miR-134 expression suppressed PGLUT1 (protein O-glucosyltransferase 1) expression and Notch signaling which was accompanied by distinct in vivo tumor growth inhibition [227]. The inhibition of miR-200b in endometrioid EC cells increased the anticancer activity of cisplatin [228]. Increased expression of miR-200b, miR-200c and miR-429 in EC was associated with cisplatin resistance, however, the binding site SNP rs1043585 A > C in the miRNA response element (MRE) of the 3’-UTR (3’ untranslated region) of their target gene AP-2x blocked the binding of miR-200b/200c/429 to the MRE of AP-2x leading to upregulated expression of the tumor suppressor AP-2x and increased cisplatin activity [229,230].

Medulloblastomas (MB) belong to the most common pediatric neoplasms of the central nervous system [231]. Expression of miR-34a in MB cells suppressed MAGE-A (melanoma associated antigen) expression and induced p53 activity associated with enhanced cisplatin efficacy [231]. Neuroblastomas (NB) originating from the sympathetic nervous system causes 15% of all pediatric cancer deaths [232]. MYCN amplified high-risk NB cells expressing miR-497 revealed downregulated cell cycle regulator WEE1, which was accompanied by enhanced apoptosis induction by cisplatin [232]. In addition, suppression of miR-520f in cisplatin-resistant NB cells (SK-N-AsCis24) led to increased NAIP (neural apoptosis inhibitory protein) expression and inhibition of cisplatin-mediated apoptosis induction [233]. In adults, gliomas represent the most lethal brain malignancies, and it was shown that miR-136 expression in glioma cells suppressed the E2F1 oncogene leading to cisplatin sensitivity in glioma cells [234].

In addition, miRNAs function as key regulators in pancreatic cancers (PaCa), and suppression of miR-374b was associated with cisplatin resistance in pancreatic cancers [235]. In addition, expression of miR-34 sensitized pancreatic cancer cells to cisplatin treatment via suppression of Bcl-2 and Notch1/2 [236]. Gallbladder cancer (GBC) is the most common cancer of the biliary tract with poor survival rates, and it was shown that expression of miR-145 increased cisplatin activity in GBC cells via downregulation of the multidrug resistance associated protein 1 (MRP1) [237].

Anaplastic thyroid carcinoma (ATC, a rare but aggressive thyroid cancer), levels of the tumor suppressor miR-30d were downregulated while induced miR-30d expression sensitized ATC cells to cisplatin treatment by suppression of Beclin-1 and inhibition of autophagic tumor cell survival [238].

The most prevalent bone cancer is osteosarcoma (OS) and high expression of miR-133a was associated with poor survival [239]. OS cells treated with cisplatin showed higher levels of miR-133a, and inhibition of miR-133a expression sensitized OS cells to cisplatin treatment [239]. The expression of miR-103 and miR-107 sensitized OS cells (U2OS) to cisplatin treatment via inhibition of homologous recombination (HR) and inhibition of the formation of RAD51 foci [240]. In addition, U2OS cells, which expressed miR-138, showed repression of histone H2AX expression, inhibition of HR repair and enhanced sensitivity to cisplatin treatment [241].

In order to investigate the role of Marek’s Disease Virus Type 1 miRNA miR-M3 (MDV1-miR-M3) from a chicken herpes virus for cisplatin sensitivity, chicken fibroblast cells (DF-1) were transfected with MDV1-miR-M3 [242]. The expression of MDV1-miR-M3 in DF-1 cells inhibited cisplatin-mediated apoptosis induction via suppression of Smad2 (mothers against decapentaplegic 2) [242]. A list of miRNAs involved in cisplatin activity in miscellaneous cancers is given in Table 9.

### 2.2. Carboplatin

Carboplatin, cis-diammine(cyclobutane-1,1-dicarboxylate-O,O’)-platinum(II), was the second platinum complex that was approved for anticancer therapy and it has shown reduced side-effects and lower toxicity than cisplatin [30]. Because of its improved toxicity profile, carboplatin has begun to replace cisplatin in various solid tumors such as ovarian cancer, lung cancer, head-and-neck cancer, and cervix carcinomas and it is given to the patients as intravenous infusions [30]. In the carboplatin molecule, the chlorido ligands of cisplatin were replaced by the O,O’-chelating ligand cyclobutane-1,1-dicarboxylate (CBDCA) which reduced the reactivity of carboplatin when compared with cisplatin [30]. Nevertheless, carboplatin formed the same DNA adducts as cisplatin and exhibited cross-resistance to cisplatin [30].

#### 2.2.1. Carboplatin, miRNAs and ovarian cancer

Patients who suffered from EOC (epithelial ovarian cancer) and received carboplatin treatment were investigated for their miRNA expression profile, and high expression of miR-181-5p as well as high phospho-Smad2 levels were associated with poor prognosis and shorter survival [243]. The ABC-transporter ABCD2 was suppressed by miR-30d in ovarian cancer cells associated with enhanced carboplatin-mediated apoptosis induction possibly via increased platinum accumulation in the cancer cells [36]. Reduced miR-148b-5p expression in EOC patients who received decitabine plus carboplatin chemotherapy exhibited shorter progression free survival [244]. In addition, carboplatin-resistance was observed from ovarian cancer cells that express miR-193b leading to suppression of CRIM1 (cysteine-rich transmembrane BMP regulator 1) [245]. The expression of the miR-200 family miRNAs miR-200c and miR-141 mimics in ovarian cancer cells led to carboplatin resistance [246]. In contrast to that, increased expression of miR-200 family miRNAs in ovarian cancer patients who received paclitaxel-carboplatin therapy was associated with improved response to chemotherapy and prolonged progression free survival because of reduction of β-tubulin III protein levels [247]. Levels of small nuclear RNA (snRNA) RNU2-1f (also described as miR-1246 and miR-1290, both miRNAs are fragmented forms of RNU2-1f) was increased in sera of EOC patients, and high RNU2-1f concentrations were associated with carboplatin-resistance in EOC patients [248]. EOC ascites tumors exhibited upregulated miR-21 and miR-21a expression as well as carboplatin resistance [249]. High levels of miR-27a were observed from platinum-resistant (cisplatin or carboplatin) ovarian cancer patients, which was associated with poor prognosis [54]. Further to this, high levels of let-7a in ovarian

| Cervical cancer | Tumor suppressors | Oncogenes |
|-----------------|------------------|-----------|
| miR-30a, miR-34a, miR-124, miR-125a, miR-506, miR-520b, miR-605 | miR-93, miR-106b, miR-181a, miR-199a, miR-125b |
| miR-29b, miR-31, miR-205 | | |

### Table 9

MicroRNA tumor suppressors and oncogenes correlated with cisplatin activity in cervical cancers and prostate cancers.
cancer patients were accompanied by weaker response to paclitaxel-carboplatin chemotherapy and shorter survival [250]. A list of miRNAs involved in carboplatin activity in ovarian cancers is given in Table 10.

2.2.2. Carboplatin, miRNAs and lung cancer

NSCLC (non-small cell lung cancer) cells with high miR-19b and low miR-146a expression were correlated with shorter survival and lymph node metastasis promotion in NSCLC patients receiving platinum-based chemotherapy (e.g., carboplatin) [251]. In addition, NSCLC patients receiving platinum therapy (either carboplatin or cisplatin) who showed partial response to platinum treatment had low levels of oncogenic miR-21 [252]. Increased levels of the oncogene miR-27a associated with poorer response to carboplatin were observed from Chinese NSCLC patients who harboured a low miR-146a expression were correlated with shorter survival and lymph node metastasis promotion in NSCLC patients receiving platinum-based chemotherapy (e.g., carboplatin) [251]. In addition, NSCLC patients receiving platinum therapy (either carboplatin or cisplatin) who showed partial response to platinum treatment had low levels of oncogenic miR-21 [252]. Increased levels of the oncogene miR-27a associated with poorer response to carboplatin were observed from Chinese NSCLC patients who harboured a single nucleotide polymorphism (SNP) in the pre-miR-27a [106]. NSCLC patients with increased levels of miR-135a*, miR-196b, and miR-1290 showed improved response to platinum-based chemotherapy (either carboplatin or cisplatin) [253]. In A549 and H1975 lung cancer cells, expression of the tumor suppressor miR-218 inhibited tumor cell growth and invasion, while expression of oncogenic miR-205 led to carboplatin resistance via upregulation of anti-apoptotic Mcl-1 and survivin as well as suppression of pro-apoptotic PARP (poly ADP ribose polymerase), caspase-3, and Bax proteins [254]. A list of miRNAs involved in carboplatin activity in lung cancers is given in Table 11.

2.2.3. Carboplatin, miRNAs and miscellaneous cancers

Carboplatin-resistant Huh-7 hepatocellular carcinoma (HCC) cells showed increased expression of miR-27b, miR-146a, miR-146b-5p, miR-181a, and miR-181d [255]. In contrast to that, the expression of miR-621 in breast cancer cells sensitized these cancer cells to carboplatin treatment via inhibition of FBXO11 and increased p53 activity [256]. In addition, increased expression of miR-218 in cervical cancer (CC) cells augmented carboplatin activity via suppression of cyclin D1 followed by cell cycle arrest [257]. In retinoblastoma (RB) cells, miR-34a inhibited HMGBl expression leading to enhanced activity of chemotherapeutic agents including carboplatin [258]. A list of miRNAs involved in carboplatin activity in miscellaneous cancers is given in Table 12.

2.3. Oxaliplatin

Oxaliplatin differs structurally from cisplatin and carboplatin, and this Pt(II) complex consists of an N,N’-chelating ligand (trans-1R,2R-diaminocyclohexane, DACH) and the O,O’-chelating ligand oxalate [30]. Due to the bulky organic DACH ligand of oxaliplatin, the DNA adducts built by oxaliplatin were more toxic when compared with cisplatin adducts and the oxaliplatin-DNA-adducts were not recognized by the DNA mismatch repair system [30]. Oxaliplatin showed no cross-resistance to cisplatin and carboplatin in colorectal cancers (CRC) which are resistant to cisplatin and carboplatin treatment [30]. Consequently, oxaliplatin was approved for the treatment of colorectal cancers and is mostly given as intravenous infusions in combination with 5-FU and folinate (= FOLFOX regimen) [30].

2.3.1. Oxaliplatin, miRNAs and colorectal cancers

Treatment of CRC (colorectal cancer) cells (HCT-8) with oxaliplatin led to suppression of six oncogenic miRNAs (miR-92a, miR-93, miR-191, miR-222, miR-1826) which likely contributed to the potent oxaliplatin activity against CRC [259]. In contrast to that, oxaliplatin-resistant CRC cells showed upregulated miR-203 expression via inhibition of ATM kinase expression [260]. MiR-153 expression also led to oxaliplatin resistance by downregulation of FOXO3a (forkhead box O3a) [261]. High levels of miR-20a were found in oxaliplatin-resistant SW620 CRC cells leading to BNIP2 (Bcl-2 adenovirus E1B 19 kDa interacting protein 2) targeting, and inhibition of miR-20a sensitized SW620 cells to oxaliplatin treatment [262]. It was found that deregulated stromal cells produced oncogenic miR-21 leading to inhibition of oxaliplatin-mediated apoptosis induction in CRC cells and to enhanced invasiveness of CRC cells via suppression of the MMP2 (matrix metalloproteinase 2) inhibitor RECK (reversion-inducing cysteine-rich protein motif with Kazal motifs) [263]. The biguanide metformin suppressed miR-21 expression in CRC cells via inhibition of Wnt signaling leading to increased oxaliplatin activity [264]. Further to this, miR-34a expression was downregulated by oxaliplatin in CRC cells, which was associated with oxaliplatin resistance [265]. Interestingly, the new and orally applicable Pt(IV) drug candidate satraplatin induced expression of the tumor suppressor miR-34a in CRC cells and, thus, may overcome platinum resistance [266]. However, another study reported of oxaliplatin-induced p53 activation and miR-34a upregulation in CRC cells, which was accompanied by downregulation of E2F1, DUT-N, and genes of the thymidylate biosynthesis leading to reduced dTTP levels [266]. Repression of the tumor suppressor let-7 family by LIN28B reduced oxaliplatin activity in CRC cells via suppression of the MMP2 (matrix metalloproteinase 2) inhibitor RECK (reversion-inducing cysteine-rich protein motif with Kazal motifs) [263]. The biguanide metformin suppressed miR-21 expression in CRC cells via inhibition of Wnt signaling leading to increased oxaliplatin activity [264]. Further to this, miR-34a expression was downregulated by oxaliplatin in CRC cells, which was associated with oxaliplatin resistance [265]. Interestingly, the new and orally applicable Pt(IV) drug candidate satraplatin induced expression of the tumor suppressor miR-34a in CRC cells and, thus, may overcome platinum resistance [266]. However, another study reported of oxaliplatin-induced p53 activation and miR-34a upregulation in CRC cells, which was accompanied by downregulation of E2F1, DUT-N, and genes of the thymidylate biosynthesis leading to reduced dTTP levels [266]. Repression of the tumor suppressor let-7 family by LIN28B reduced oxaliplatin activity in CRC cells (HCT-116, SW480) as well [267]. Expression of miR-133a increased oxaliplatin-induced apoptosis in CRC cells by suppression of RFLF (ring finger and FYVE-like domain containing E3-ubiquitin protein ligase) [268]. Oxaliplatin activity was also increased by miR-139-5p via suppression of anti-apoptotic Bcl-2 protein expression [269]. Oxaliplatin-resistant CRC cells were sensitized to oxaliplatin treatment by increased miR-297 levels, which reduced the levels of the platinum-resistance associated MRP2 (MDR-associated protein 2) protein in the CRC cells [270]. Expression of miR-1915 sensitized oxaliplatin-resistant CRC cells (HCT-116/L-OHP) to oxaliplatin treatment by downregulation of anti-apoptotic Bcl-2 protein expression [271]. In addition, expression of miR-1915 and miR-1914 increased the activity of oxaliplatin.

Table 9

| Tumor suppressors | Oncogenes |
|-------------------|-----------|
| miR-30d (ATC), miR-34 (PaCa), miR-34a (MB), miR-103 (OS), miR-107 (OS), miR-134 (EC), miR-136 (glioma), miR-138 (OS), miR-145 (CRC), miR-302a (TGCT), miR-374b (PaCa), miR-383 (TGCT), miR-497 (NB), miR-520f (NB) | miR-133a (OS), miR-200b (EC), miR-200b* (EC), miR-200c (EC), miR-429 (EC), MDV1-miR-M3 (chicken fibroblasts) |

Table 10

| Tumor suppressors | Oncogenes |
|-------------------|-----------|
| miR-30d, miR-148b-5p, miR-200 family(1) | let-7a, miR-21, miR-27a, miR-141, miR-181-5p, miR-193b*, miR-200c(1), miR-214, RNU2-1f (miR-1246, miR-1290) |
in resistance CRC cells by suppression of NFIX (nuclear factor I/X) [272].

Rectal cancer patients who responded well to oxaliplatin-capcitabine radiochemotherapy (i.e., who showed complete response) exhibited upregulated miR-622 and miR-630 expression [273]. In addition, patients suffering from metastatic CRC showed better responses to XELOX therapy (combination of capcitabine/ xeloda and oxaliplatin) and longer progression-free survival in case of high miR-126 levels [274]. Overexpression of miR-107 and miR-99a-3p was associated with improved outcome in patients with metastatic CRC treated with 5-FU and oxaliplatin [275]. Advanced CRC patients with low miR-148a expression showed poorer survival and worse response to oxaliplatin treatment [276]. In addition, patients suffering from KRAS-mutated CRC with increased miR-200b and reduced miR-146 levels exhibited longer survival times after treatment with oxaliplatin in combination with capcitabine and the antibody cetuximab [277]. Upregulation of miR-196b-5p and miR-592 also increased the potency of the XELOX regimen in metastatic CRC patients [278]. In contrast to that, upregulated expression of five serum miRNAs (miR-20a, miR-130, miR-145, miR-215, miR-372) was observed from oxaliplatin-resistant CRC patients [279]. However, upregulated miR-143 and miR-145 enhanced activity of oxaliplatin in CRC cells by suppression of CD44 (cluster of differentiation 44), KRAS, KLF5 (Krüppel-like factor 5) and BRAF (v-Raf murine sarcoma viral oncogene homolog B1) [280]. In addition, higher expression of miR-106a, miR-130b and miR-484 was determined in patients with oxaliplatin-resistant CRC when compared with responders [281]. Increased expression of miR-320e also led to worse outcome in advanced CRC patients who received oxaliplatin treatment [282]. Further to this, overexpression of miR-27b, miR-181b, and miR-625-3p was discovered in non-responding metastatic CRC patients after treatment with oxaliplatin (XELOX or FOLFOX) and these three oncogetic miRNAs were also upregulated in oxaliplatin-resistant CRC cells (HCT-116/oxPt) [283]. A list of miRNAs involved in oxaliplatin activity in colon cancers is given in Table 13.

### 2.3.3. Oxaliplatin, microRNAs and miscellaneous cancers

The combination of gemcitabine and oxaliplatin showed only slight benefits in hepatocellular carcinoma (HCC) patients. UCP2 (mitochondrial uncoupling protein 2) expression in HCC patients was identified as resistance factor for chemotherapy in HCC patients, while induced expression of miR-214 reduced the UCP2 levels in HCC and inhibited HCC growth [289]. In contrast to that, expression of miR-93 increased oxaliplatin resistance in hepatoma cells by suppression of PTEN [290]. In oxaliplatin-resistant pancreatic cancer cells (AsPc-10R), the expression of miR-21 and platinum (cisplatin or oxaliplatin) therapy was associated with reduced expression of miR-99b, miR-145*, miR-451, and miR-505* in patients suffering from esophageal adenocarcinoma (EAC) [158]. MiRNA polymorphisms also play a role for oxaliplatin resistance and reduced survival of esophageal squamous cell carcinoma (ESCC) patients receiving platinum-based therapy (cisplatin or oxaliplatin) were correlated to the TT genotypes of miR-196a2 rs11614913 and miR-125a rs12976445 [162].

The oncogetic miR-21 and miR-181b were strongly expressed in advanced gastric cancer tissues (GC), and advanced GC patients with suppressed expression of miR-21 and miR-181b exhibited better response to oxaliplatin and prolonged survival [284]. In addition, metastatic or recurrent GC patients with high levels of miR-1 and miR-27a showed lower response rates and shorter overall survival after 5-FU/oxaliplatin chemotherapy [285]. Another study reported of suppression of miR-20b, miR-27a, and miR-181a accompanied by increased expression of MDR1, HIF1A (hypoxia-inducible factor 1-alpha) and HIPK2 (homeodomain-interacting protein kinase 2) in GC patients with progressing disease when compared with responders to EOX chemotherapy (epirubicin, oxaliplatin, capcitabine) [286]. In addition, patients suffering from advanced GC revealed better responses to oxaliplatin treatment when the miR-129 expression level was low [287]. GC patients who received palliative chemotherapy (5-FU in combination with platinum complexes, cisplatin or oxaliplatin) showed shorter time to progression in association with overexpression of five miRNAs (miR-150, miR-342-3p, miR-181b, miR-221, miR-224) and suppression of miR-520 h, while shorter overall survival was associated with increased expression of miR-150, miR-192, miR-224, miR-375, and miR-342-3p [288]. A list of miRNAs involved in oxaliplatin activity in esophageal and gastric cancers is given in Table 14.

### Table 11

| Tumor suppressors | Oncogenes |
|-------------------|-----------|
| miR-139a, miR-146a, miR-1826, miR-218, miR-1290 | miR-19b, miR-21, miR-27a, miR-205 |

### Table 12

| Tumor suppressors | Oncogenes |
|-------------------|-----------|
| miR-34a (BB), miR-218 (CC), miR-621 (breast cancer) | miR-27b (HCC), miR-146a (HCC), miR-146b-5p (HCC), miR-181a (HCC), miR-181d (HCC) |

### Table 13

| Tumor suppressors | Oncogenes |
|-------------------|-----------|
| let-7 family, miR-34a, miR-99a-3p, miR-107, miR-126, miR-133a, miR-139-5p, miR-143, miR-145*, miR-148a, miR-196b-5p, miR-200b, miR-297, miR-592, miR-622, miR-630, miR-1914*, miR-1915 | miR-20a, miR-21, miR-27b, miR-92a, miR-93, miR-106a, miR-130, miR-130b, miR-145*1, miR-146, miR-153, miR-181b, miR-191, miR-197, miR-203, miR-216, miR-222, miR-320a, miR-327, miR-484, miR-625-3p, miR-1826 |
miR-221 was twice as high as in the AsPc-1 parental cells leading to suppression of PTEN, PDCD4, Maspin and TPM1 (trompomyosin 1) [291].

2.4. MiRNAs modulated in various platinum-sensitive and resistant cancers as drugs or drug targets

The expression of certain miRNAs was modulated in various platinum-resistant or platinum-treated cancers and, thus, these miRNAs feature suitable drug targets (Table 15). Concerning tumor suppressor miRNAs, tumors expressing let-7 family miRNAs (let-7c, let-7g, let-7i), miR-16, miR-20b, miR-29b, miR-30d, miR-34a, miR-107, miR-196b, miR-218, miR-497, miR-503 and miR-199a, miR-200a, miR-200b, miR-27a(!), miR-181a, miR-181b, miR-192, miR-221, miR-224, miR-342-3p, miR-374a, miR-425 increased platinum anticancer activity. In addition, certain oncogenic miRNAs are involved in various platinum-resistant cancers, such as miR-10a, miR-21, miR-24, miR-99b, miR-106a, miR-125b, miR-150, miR-191, miR-192, miR-214, miR-221, miR-222, miR-224, miR-374a, and miR-425. The inhibition of these oncomirs by potent miRNA antagonists (antagomirs) represents another target for improved platinum-based chemotherapy. Numerous miRNAs such as miR-27a, miR-31, miR-93, miR-98, miR-101, miR-128, miR-130, miR-133a, miR-138, miR-141, miR-145, miR-146a, miR-146b, miR-145, miR-199a, miR-200a, miR-203, miR-205, miR-375, miR-429, miR-451, miR-630, miR-638, miR-642, miR-1290 and members of the miR-200 family are either tumor suppressors or oncomirs depending on the cancer type.

The quick and facile degradation of RNA molecules as well as their low cell permeability limited the application of accurate miRNAs (either mimics or antagonirs) for anticancer therapy. The liposomal formulation MRX34 of a tumor suppressor miRNA-34a mimic (Mirnarx Therapeutics) showed adequate stability and cell delivery of the applied miRNA-34a mimic and led to the initiation of phase I clinical trials with MRX34 [292]. Since miR-34a augmented the anticancer activity of cisplatin, carboplatin and oxaliplatin, the combination of MRX34 with platinum complexes appears to be promising for future clinical trials of various solid tumor diseases. Further to this, an increased lipophilicity of RNA molecules was generated by modification with locked nucleic acids (LNA). LNAs possess a methylene bridge between the 2'-oxygen and the 4'-carbon of the ribose moiety and a prominent example of an LNA-modified antagonist is Miravirsen (developed by Santaris Pharma), which targets miR-122 expressed in the human liver [292]. In addition, several dietary factors and natural products that are easily obtained from natural sources provide a rich supply of low-cost, safe and easily available miRNA-modulators for the improvement of platinum-based chemotherapy [29,293].

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