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Relations between approved platinum drugs and non-coding RNAs in mesothelioma

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ABSTRACT

Malignant mesothelioma diseases feature an increasing risk due to their severe forms and their association with asbestos exposure. Platinum(II) complexes such as cisplatin and carboplatin are clinically approved for the therapy of mesothelioma often in combination with antimetabolites such as pemetrexed or gemcitabine. It was observed that pathogenic properties of mesothelioma cells and the response of mesothelioma tumors towards platinum-based drugs are strongly influenced by non-coding RNAs, in particular, by small microRNAs (miRNAs) and long non-coding RNAs (lncRNAs). These non-coding RNAs controlled drug sensitivity and the development of tumor resistance towards platinum drugs. An overview of the interactions between platinum drugs and non-coding RNAs is given and the influence of non-coding RNAs on platinum drug efficacy in mesothelioma is discussed. Suitable non-coding RNA-modulating agents with potentially beneficial effects on cisplatin treatment of mesothelioma diseases are mentioned. The understanding of mesothelioma diseases concerning the interactions of non-coding RNAs and platinum drugs will optimize existing therapy schemes and pave the way to new treatment options in future.

1. Introduction

Mesothelioma features an aggressive tumor disease with high mortality rates (median survival of ca. 1 year after diagnosis) and ca. 40.000 deaths per year worldwide [1]. Malignant pleural mesothelioma (MPM) derives from the pleura tissue covering the lungs and comprises ca. 80% of all diagnosed mesotheliomas [2]. Further rare mesothelioma diseases are represented by peritoneal mesothelioma, pericardial mesothelioma, and tunica vaginalis mesothelioma [2]. MPM itself can be subdivided into three different histological forms, the most common epitheloid mesothelioma (50–70%, similar to carcinomas), sarcomatoid mesothelioma (10–20%, similar to sarcomas) and biphasic mesothelioma (30%, which displays a mixture of epitheloid and sarcomatoid cell forms) [3]. Sarcomatoid and biphasic forms are more aggressive and less sensitive to chemotherapy than epitheloid mesotheliomas and showed worse prognosis than epitheloid mesotheliomas [4]. In advanced stages of MPM associated with distinctly worse prognoses metastases can occur in lung, lymph nodes, muscles, chest wall, peritoneum, pericardium, bones, liver, and brain [5]. A group of carcinogenic silicate fibers commonly known as asbestos was identified as the most frequent reason for the development of mesothelioma [6]. The number of mesothelioma patients will probably rise in future mainly among male persons exposed to asbestos during their daily work and ca. 125 million people worldwide are exposed to asbestos every year [7]. The remarkably long time between asbestos exposure and the development of MPM (between 25 and 70 years after exposure) is unique and, thus, the vast majority of MPM patients is 60 years old and older [8,9]. Other reasons for the development of mesothelioma diseases comprise the exposure to the carcinogenic silicate fiber erionite (a non-asbestos fiber), exposure to zeolite and fiberglass, SV40 virus infection, tuberculosis, radiation, and genetic disposition, while the reason for the high occurrence of peritoneal mesothelioma among young Chinese women from the Eastern Chinese province Zhejiang is still uncovered [10,11].

The carcinogenic effects of asbestos fibers casually accompanied by other factors such as SV40 virus infection and genetic disposition (BAP1

Abbreviations: ABC, ATP-binding cassette; AKBA, 3-acetyl-11-keto-β-boswellic acid; AKI, acute kidney injury; Bcl-2, B-cell lymphoma 2; CAF, cancer-associated fibroblast; CBDCA, cyclobutane-1,1-dicarboxylate; DADS, diallyl sulfide; DHA, docosahexaenoic acid; DIM, 3,3′-diindolylmethane; DMPM, diffuse malignant peritoneal mesothelioma; EGCG, epigallocatechin-3-gallate; EMT, epithelial-mesenchymal transition; HOTAIR, HOX transcript antisense RNA; RA, retinoic acid; I3C, indole-3-carbinol; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; MPM, malignant pleural mesothelioma; MRP1, multidrug resistance protein 1; NaB, sodium butyrate; NSCLC, non-small cell lung cancer; PEG, polyethylene glycole; PEITC, phenethylisothiocyanate; PDCD4, programmed cell death 4; PTEN, phosphatase and tensin homolog; SAHA, suberoylanilide hydroxamic acid; SFN, sulforaphane; TNBC, triple-negative breast cancer; TSA, trichostatin A

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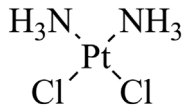
mutation or inactivation) induce inflammation processes including the expression of catalytically active 5-LOX, enhanced Akt, Notch, VEGFR and EGFR signaling, and other immunological factors [12,13]. Cell necrosis caused by asbestos releases HMGB1 to the extracellular space, which triggers an inflammation response in macrophages and mesothelial cells leading to enhanced mesothelial cell transformation [13]. Aside altered protein expression, the levels of non-coding RNAs are often changed as well. Differences in miRNA expression were observed from mesothelioma cells when compared with benign samples and certain circulating miRNAs were identified in mesothelioma patients [13,14]. Meanwhile, miRNAs were identified as prognostic factors, as potential therapeutic targets and as therapeutic agents [14]. In particular, several miRNAs were identified which induce oncogenes (let-7, miR-9, miR-7-1, miR-15, miR-16, miR-34b/c, miR-203), inhibit apoptosis (miR-1, miR-17-92) and/or activate signaling pathways (miR-29c, miR-31, miR-34b/c, miR-126, miR-200) [15].

Indeed, there are only very few treatment options for mesothelioma patients at the moment. Surgery and radiation therapy is often difficult and no good option because of the problematic location of the primary tumors near vital organs [16,17]. Systemic platinum-based chemotherapy is often applied instead. Initially, cisplatin was solely applied frequently as first-line treatment but meanwhile a combination of cisplatin and pemetrexed initially tested by Vogelzang et al. is given in most cases as a distinctly more efficient first-line therapy of MPM [16,18]. In case that cisplatin is too toxic (in particular, too nephrotoxic) or the patient has pertinent pre-existing illnesses, cisplatin can be practically replaced by the much less toxic platinum complex carboplatin [19]. More recently, the combination of cisplatin or carboplatin, and pemetrexed with the VEGFR-inhibitor bevacizumab was claimed as a superior first-line therapy of MPM than the currently applied platinum plus pemetrexed therapy [20,21].

Non-coding RNAs such as microRNAs (miRNAs, highly conserved small RNAs of 22–23 nucleotides) are suitable tools to investigate the modes of drug resistance and activity in order to design improved therapy options for mesothelioma treatment [22,23]. Particularly short survivors of MPM displayed higher expression of miR-21–5p, miR-221–3p, and the miR-17-92 cluster (miR-17–5p, miR-20a-5p) associated with drug resistance and regulation of Hippo signaling, PI3K/Akt signaling and focal adhesion when compared with long survivors [23]. The biology of especially drug-resistant cancer stem-like cells is regulated by non-coding RNAs [24]. It was shown that the anticancer activity of platinum complexes was strongly regulated by miRNAs [25]. There are tumor suppressor miRNAs and oncogenic miRNAs (so-called oncomirs), and the mature miRNAs can regulate various genes by inhibition of the translation of target messenger RNAs (mRNAs) via binding to the 3′-untranslated region (3′UTR) of the target mRNA [26–28]. The clinical phase 1 trial with MPM patients treated with miRNA-16 mimic miRNA loaded minicells called TargomiR showed an acceptable safety profile and moderate clinical response, which may be improved by combination with other chemotherapeutic drugs or immune checkpoint inhibitors [29]. In addition to miRNAs, there are long non-coding RNAs (lncRNAs, defined as RNA molecules of more than 200 nucleotides) present in large numbers in the genome, which are of growing importance for the understanding of cancer diseases [30]. Many lncRNA genes have two exons and ca. 60% of the known lncRNA molecules have a poly-A tail [30]. Most lncRNAs are involved in chromatin remodeling, gene regulation and inhibition of smaller miRNA molecules [30,31]. The connection of various lncRNAs with the Wnt signaling pathway is particular intriguing [32]. This review provides an overview of the interactions of non-coding RNAs with the platinum complexes cisplatin and carboplatin, which are currently approved for mesothelioma therapy. The beneficial potential of various non-coding RNA modulating agents on cisplatin therapy of mesothelioma diseases is discussed.



Cisplatin

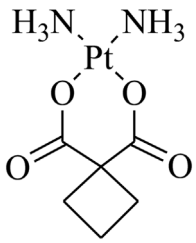


Fig. 1. Structures of the clinically approved platinum(II) complexes cisplatin and carboplatin.

2. Platinum complexes and their interactions with non-coding RNAs in mesothelioma

2.1. Cisplatin and carboplatin

Cisplatin, *cis*-(diammine)dichloridoplatinum(II), became the first platinum complex that was approved for anticancer therapy in the USA in 1978 after its biological activity had been discovered in 1969 (Fig. 1) [33,34]. Mechanistically, *S*− and *N*-bionucleophiles of proteins and nucleic acids (in particular, the N7-atom of guanine bases) in the cancer target cells replace the chlorido ligands of the square-planar complex cisplatin leading to toxic DNA crosslinks (e.g., 1,2-intrastrand crosslinks) and to the induction of apoptosis very often in a p53-dependent way [34–36]. In order to avoid chlorido ligand exchange in the infusion solution cisplatin is given to cancer patients as intravenous chloride infusions [34]. Cisplatin is one of the most potent cancer therapeutics and it is clinically applied against various tumor diseases including testicular cancer (where it shows a particularly high curing rate), ovarian cancer, cervix carcinoma, breast cancer, prostate carcinoma, endometrial cancer, bladder cancer, lung cancer (both NSCLC and SCLC forms), melanoma, various sarcomas, and head-and-neck cancer [34,37]. However, severe side-effects and the formation of drug resistance limit the application of cisplatin [38,39].

The second platinum complex approved for anticancer therapy was carboplatin, *cis*-diammine(cyclobutane-1,1-dicarboxylate-*O*,*O*′)platinum(II), which has shown distinctly lower toxicity and reduced side-effects than cisplatin (Fig. 1) [34]. The *O*,*O*′-chelating ligand cyclobutane-1,1-dicarboxylate (CBDCA) of carboplatin replaced the chlorido ligands of cisplatin which reduced the reactivity of carboplatin when compared with cisplatin [34]. However, DNA adducts similar to cisplatin-adducts were also formed by carboplatin and cross-resistance to cisplatin was observed for carboplatin [34]. Further direct interactions of cisplatin and carboplatin with cancer-relevant ribonucleic acids such as non-coding RNAs are conceivable. Meanwhile, carboplatin has replaced cisplatin in the treatment of various tumor diseases (e.g., ovarian cancer, lung cancer, head-and-neck cancer, and cervix carcinomas) because of its better tolerability [34]. In these cases, intravenous infusions of carboplatin are given to the patients [34].

2.2. Cisplatin, non-coding RNAs and mesothelioma

Several miRNAs were identified which regulate mesothelioma cell sensitivity to cisplatin treatment (Fig. 2). The effects are often tumor-dependent. The upregulation of the oncomir miR-31 induced cisplatin resistance in ovarian cancer and NSCLC cells (the latter associated with ABCB1 transporter suppression), while suppression of miR-31 in

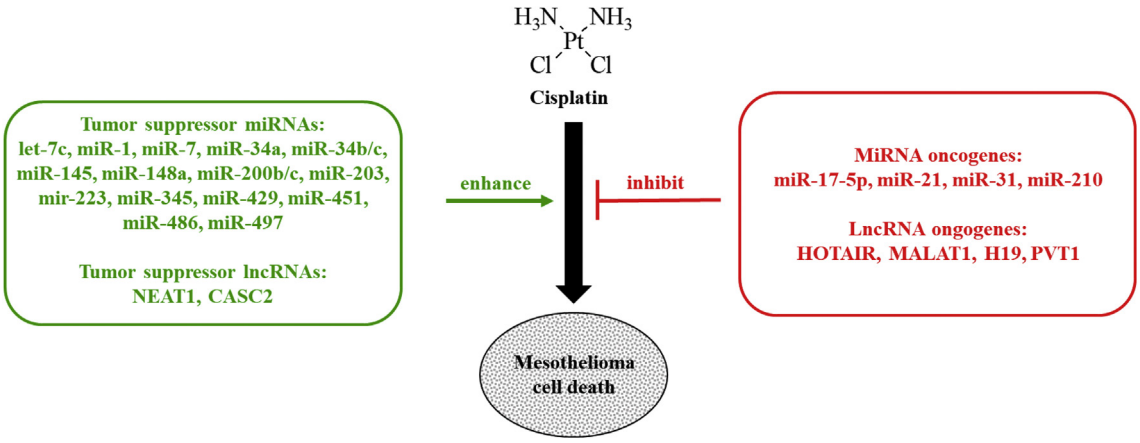


Fig. 2. Cisplatin and non-coding RNAs in mesothelioma.

prostate cancer cells led to cisplatin resistance [40–42]. In MPM cells, the expression of miR-31 induced increased resistance to cisplatin, however, a higher platinum content was identified in the cells with high miR-31 expression which was accompanied by a reduced intra-nuclear platinum content [43]. An indirect up-regulation of the transporter ABCB1 by miR-31 (via OCT1 down-regulation) associated with drug accumulation in lysosomes was discovered although direct ABCB1 up-regulation led to cisplatin sensitivity like in NSCLC cells [41,43]. Thus, miR-31 prompts cisplatin resistance in MPM cells via an ABCB1-independent mode [43]. Chemotherapy of cisplatin in combination with pemetrexed (see below) led to differences in the expression of certain miRNAs in MPM tissues when compared with samples from non-neoplastic pleura tissues [44]. MiR-126, miR-143, miR-145 and miR-652 were down-regulated in biopsies or resected MPM tumors when compared to non-neoplastic pleura while the difference of the suppression of these miRNAs was less strong in resected MPM tumor samples after applied cisplatin/pemetrexed chemotherapies [44]. Thus, these miRNAs may feature diagnostic biomarkers for the detection of MPM. In addition, cisplatin/pemetrexed treatment up-regulated let-7c, miR-486–5p and miR-451 distinctly while miR-210 was significantly down-regulated when compared with chemotherapy-naïve biopsies [44]. In the case of miR-210, its expression was correlated with poor prognosis in MPM patients undergoing extrapleural pneumonectomy and cisplatin-resistant laryngeal cancer cells showed up-regulated miR-210 whose targets were NUPR1, HTRA1 and RGS10 associated with drug resistance [45,46]. In contrast to that, let-7c as a component of the miR-99a/let-7c/miR-125b cluster worked as a tumor suppressor in MPM [47]. In NSCLC, let-7c inhibited migration and invasion via ITGB3 and MAP4K3 targeting and the expression of let-7c re-sensitized cisplatin-resistant lung cancer cells (by suppression of ABCC2-transporter and Bcl-xl) and induced EMT reversal while let-7c was down-regulated in other cisplatin-resistant cancer types including resistant ovarian cancers and esophageal squamous cell carcinomas [48–52]. Similarly, miR-486 expression was correlated with increased survival of patients suffering from MPM (miR-486 targets tumorigenic ARHGAP5 in lung cancer) [53]. In NSCLC patients, the suppression of miR-451 (targets PSMB8, MIF, and ERCC1) was linked with bad prognosis and miR-451 expression increased cisplatin activity and suppressed Wnt and Akt signaling in lung cancer cells [54–56].

Further miRNAs may play a crucial role concerning cisplatin activity against MPM. The thoroughly investigated oncomir miR-21 was overexpressed in MPM and repressed its target, the tumor suppressor PDCD4 (programmed cell death 4) in MPM [57]. It is likely that miR-21 also plays a key role for cisplatin resistance in MPM since it was shown to do so in platinum-resistant NSCLC cells and patients by repression of PTEN (phosphatase and tensin homolog) and induction of anti-apoptotic Bcl-2 (B-cell lymphoma 2) [58]. MiR-34s were shown to regulate a variety of cancers and the suppression of miR-34s transformed non-malignant mesothelial cells into oncogenic cells [59]. The relatively bad response of diffuse malignant peritoneal mesothelioma (DMPM) to chemotherapy was correlated with suppression of miR-34a, which has shown antiproliferative effects by suppression of c-MET and AXL in DMPM [60]. Bladder cancer treated with cisplatin showed upregulated levels of miR-34a leading to cancer cell sensitivity to chemotherapy [61]. In lung tumors, restored miR-34a expression increased the survival of KP mice treated with cisplatin and down-regulation of PEBP4 in lung cancer cells by miR-34a led to enhanced cisplatin activity [62,63]. Indeed, miR-34a re-sensitized lung cancer cells to cisplatin treatment independent of their p53 state [64]. Methylation of the tumor suppressor miR-34b/c, a target of the important transcription factor p53 involved in DNA-damage response, suppressed miR-34b/c activity and led to tumorigenesis in MPM [65]. Increased miR-34b/c expression led to antiproliferative effects, cell cycle arrest in the G1 phase and reduced migration of MPM cells while simple p53 overexpression showed no effects [65]. Restoration of miR-34b/c induced modest re-sensitization to cisplatin in lung adenocarcinoma [66]. MiR-223 features another miRNA suppressed in MPM, which played a role concerning cell motility and led to induction of stathmin [67]. In triple-negative breast cancer (TNBC), miR-223 expression enhanced the activity of cisplatin and doxorubicin by regulation of HAX-1 [68]. Members of the miR-200 family (miR-200b, miR-200c, miR-141, miR-429) with many predicted targets of the Wnt signaling pathway were also down-regulated in MPM when compared with lung adenocarcinoma [69]. MiR-200b and miR-200c suppression was associated with cisplatin resistance. MiR-200b expression re-sensitized lung cancer cells to cisplatin treatment and reverted epithelial-mesenchymal transition (EMT) [50]. The induction of anti-apoptotic Bcl-2 and XIAP was a result of miR-200bc/429 cluster suppression in cisplatin-resistant A549/DDP NSCLC cells, and cisplatin–mediated apoptosis induction was correlated with miR-200bc/429 expression [70]. Cisplatin activity in NSCLC cells was restored via miR-200c expression followed by *E*-cadherin induction and *N*-cadherin suppression [71]. MiR-214 levels were also low in mesothelioma cells and induced expression of miR-214 exerted anti-proliferative and anti-migratory effects via down-regulation of PIM1 [72]. Enhanced cisplatin activity was observed, for example, from cervix cancer cells showing miR-214 expression while in ovarian cancer and other cancers miR-214 expression was associated with cisplatin resistance [25,73,74]. Survivin-regulating miR-203 was also suppressed in MPM [75]. In NSCLC cells, miR-203 expression inhibited tumor cell growth, induced apoptosis, and increased the activity of cisplatin by suppression of DKK1 [76]. MiR-345 is highly expressed in malignant mesothelioma samples and its expression may contribute to enhanced cisplatin activity by suppression of the ABC-transporter MRP1, which was associated with multidrug resistance [77–79]. In addition to miR-345, miR-7 features

another MRP1-targeting miRNA, which is overexpressed in MPM and may contribute to cisplatin sensitivity in MPM as well [78,80]. MiR-148a is highly expressed in malignant mesothelioma and its cisplatin sensitizing effects were identified in renal cancer cells basing on Rab14 targeting [81,82]. In contrast to that, miR-497 was down-regulated in MPM cells and involved in cisplatin activity in NSCLC cells by regulation of Bcl-2 [80,83]. MiR-1 was shown to induce apoptosis in MPM cells and was downregulated in MPM tumor samples when compared with non-malignant samples [84]. SDF-1, a factor associated with cisplatin resistance, was suppressed by miR-1 expression in cancer-associated fibroblasts (CAFs) found in NSCLC [85]. Another tumor suppressor of MPM is represented by miR-145, which is lost in MPM and acts by downregulation of OCT4 and ZEB1 [86]. Cisplatin and paclitaxel upregulated the miR-145 level in bladder cancer cells while miR-145 expression sensitized gallbladder cancer to cisplatin by MRP1 suppression [87,88]. In contrast to that, miR-17–5p expression was high in short survivors of MPM and suppression of miR-17–5p targeting p21 led to increased cisplatin sensitivity of gastric cancer cells [23,89].

MicroRNAs can also be applied to identify severe side-effects of cisplatin during and after cisplatin therapy. For instance, acute kidney injury (AKI) in cisplatin-treated MPM patients was correlated with increased miR-21, miR-200c and miR-423 levels [90]. A list of miRNAs involved in cisplatin resistance and sensitivity of mesothelioma is given in Table 1.

The expression of lncRNAs in MPM patients was investigated in correlation with induction chemotherapy, which usually means a cisplatin-based therapy [91]. The lncRNAs AK130275, EF177379 (NEAT1) and AF268386 were upregulated in MPM tumors when compared with non-malignant pleura, but reduced levels of AK130275 and AF268386 were identified in patients receiving induction chemotherapy [91]. In addition, patients with high EF177379 expression had prolonged overall survival times in case they haven't received induction chemotherapy because induction chemotherapy lowered the EF177379 levels as well [91]. HOTAIR (HOX transcript antisense RNA) and MALAT1 (metastasis-associated lung adenocarcinoma transcript 1) feature further lncRNAs with strong relevance for mesothelioma [92]. The sarcomatoid mesothelioma subset of the Bueno NGS dataset showed upregulated HOTAIR and MALAT1 expression associated with shorter survival times [92]. In lung adenocarcinoma cells, expression of HOTAIR led to cisplatin resistance by suppression of $p21^{WAF1/CIP1}$ [93]. Similarly, MALAT1 expression induced cisplatin resistance by induction of MRP1 and MDR1 expression and activation of STAT3 transcription factor [94]. H19 lncRNA was also upregulated in sarcomatoid mesothelioma subgroups and H19 expression was shown to induce cisplatin resistance in lung cancer cells [92,95]. In addition, PVT1-knockdown enhanced cisplatin sensitivity in MPM cells by upregulation of pro-apoptotic LTB (lymphotoxin beta), BCL2L14 (Bcl-2 like protein 14), FASLG (FS ligand) and TNFRSF1B (tumor necrosis factor receptor superfamily member 1B) as well as suppression of anti-apoptotic BCL2L1, BCL2, ICEBERG (Caspase 1 inhibitor), and BIRC8 (Baculoviral IAP repeat-containing protein 8) [96]. Another lncRNA, CASC2, was downregulated in sarcomatoid MPM subgroups and expression of CASC2 in NSCLC cells increased cisplatin activity by suppression of miR-18a and miR-21 as well as induction of PTEN expression [92,97]. A list of long non-coding RNAs that may be involved in cisplatin resistance and sensitivity of mesothelioma is given in Table 2.

Table 2
Long non-coding RNA (lncRNA) tumor suppressors and oncogenes in mesothelioma proven or strongly assumed to be correlated with cisplatin activity.

lncRNA	Target(s)	Function
EF177379 (NEAT1)	-	tumor suppressor
HOTAIR	$p21^{WAF1/CIP1}$	oncogene
MALAT1	MRP1, MDR1	oncogene
H19	–	oncogene
PVT1	LTB, BLC2L14, FASLG, TNFRSF1B, BCL2L1, BCL2, ICEBERG, BIRC8	oncogene
CASC2	miR-18, miR-21, PTEN	tumor suppressor

2.3. Cisplatin and suitable combination drugs from the non-coding RNA point of view

As mentioned above, several miRNAs correlated with cisplatin sensitivity or resistance were identified in mesothelioma. Thus, suitable combination drugs with cisplatin should increase the expression of tumor suppressor miRNAs known to sensitize mesothelioma cells to cisplatin treatment or downregulate oncomirs associated with formation of cisplatin resistance. Most of these drugs are derived from natural sources or at least inspired by nature (Fig. 3).

2.3.1. Phenolic compounds

Various phenolic and polyphenolic natural products are able to regulate miRNAs correlated with cancer diseases. Epigallocatechin-3-gallate (EGCG) is a thoroughly investigated catechin polyphenol of the tea plant (*Camellia sinensis*) and well known for its positive effects on the cisplatin activity against cancer cells [98,99]. It has to be mentioned

Table 1
MicroRNA tumor suppressors and oncogenes in mesothelioma proven or strongly assumed to be correlated with cisplatin activity.

miRNA	Target(s)	Function	Expression[a]
let-7c	ITGB3, MAP4K3	tumor suppressor	lower in short survivors
miR-1	PIM1	tumor suppressor	lower
miR-7	MRP1	tumor suppressor	higher
miR-17-5p	p21	oncomir	higher in short survivors
miR-21	PDCD4, PTEN	oncomir	higher
miR-31	OCT1	oncomir	higher in short survivors
miR-34a	c-MET/Akt	tumor suppressor	lower
miR-34b/c	Bcl-2	tumor suppressor	lower
miR-145	OCT4	tumor suppressor	lower
miR-148a	Rab14	tumor suppressor	higher
miR-200b/c	Bcl-2, Wnt signaling	tumor suppressor	lower
miR-203	DKK1	tumor suppressor	lower
miR-210	NUPR1, HTRA1, RGS10	oncomir	higher in short survivors
miR-223	STMN1, HAX1	tumor suppressor	lower
miR-345	MRP1	tumor suppressor	higher
miR-429	Bcl-2, Wnt signaling	tumor suppressor	lower
miR-451	PSMB8, MIF, ERCC1	tumor suppressor	lower
miR-486	ARHGAP5	tumor suppressor	lower in short survivors
miR-497	Bcl-2	tumor suppressor	lower

[a] Expression in mesothelioma when compared with non-malignant/benign samples or other tumors.

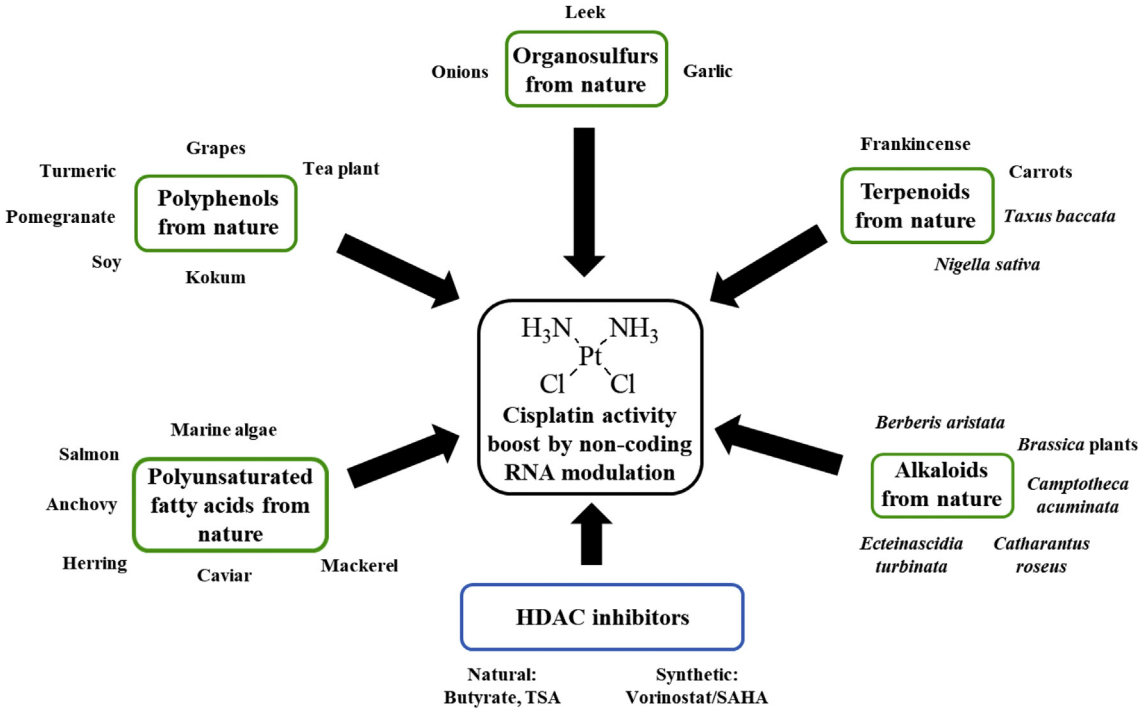


Fig. 3. Non-coding RNA modulating agents with relevance to cisplatin activity.

that high doses of EGCG (800 mg/day and more) can lead to an increase of serum transaminases as a sign of some sort of hepatotoxicity [100]. In addition, the combination of EGCG with boronic acid-based anticancer drugs such as bortezomib led to drug inactivation due to the reaction of the boronic acid moiety of bortezomib with the gallate scaffolds of EGCG [100,101]. Concerning a modulation of miRNAs with relevance to cisplatin activity, EGCG was shown to increase the expression of let-7c, miR-1, miR-7-1, miR-34a, and miR-34b while EGCG suppressed the oncomirs miR-21 and miR-210 [102–107]. EGCG also enhanced cisplatin activity in lung cancer cells by induction of expression of the tumor suppressor lncRNA NEAT1 by upregulation of CTR1 [108]. Genistein, an isoflavone from soy (*Glycine max*), downregulated the oncomir miR-21 and so do other flavanoids such as glyceollins, 3,6-dihydroxyflavone (3,6-DHF), and silibinin, while the tumor suppressor miR-34a was upregulated by genistein, glyceollins, 3,6-DHF, and quercetin [109–115]. Genistein and silibinin also induced the expression of the tumor suppressor miR-200c [113,116]. In addition, genistein suppressed oncogenic HOTAIR [117,118]. Curcumin (diferuloylmethane), another natural polyphenol from the rhizome of turmeric (*Curcuma longa*), upregulated miR-7, miR-34a, miR-145, miR-200b/c, and miR-203, and suppressed oncogenic miR-17–5p and miR-21 [119–126]. Curcumin also inhibited HOTAIR-dependent metastasis formation and suppressed the expression of the oncogenic lncRNAs H19 and PVT1 [127–129]. (Semi-)Synthetic derivatives of curcumin such as CDF and EF24 also suppressed the oncomir miR-21, and CDF additionally suppressed miR-210 [122,130–133]. The natural stilbene resveratrol found in grapes and berries also suppressed miR-21 and induced the expression of the tumor suppressors miR-34a, miR-34c, and miR-200c [134–138]. MiR-200c expression was also induced by pterostilbene, a close analog of resveratrol [133]. Further to this, resveratrol induced the expression of the tumor suppressor lncRNA NEAT1 and suppressed oncogenic MALAT1 in cancer cells [139,140]. The natural trihydroxy-anthraquinone emodin induced miR-34a and miR-429 while it suppressed miR-210 [141–143]. The natural bisphenols magnolol and honokiol induced the expression of miR-34a (honokiol) and miR-200c (magnolol) [144,145]. The polycyclic polyprenylated acylphloroglucinol (PPAP) garcinol features another interesting natural product, which was isolated from plums of the kokum tree (*Garcinia indica*) and suppressed oncogenic miR-21 while it activated the expression of tumor suppressing miR-200b and miR-200c [146,147]. Tumor suppressor miRNA expression was induced by further polyphenols such as glabridin (miR-148a), caffeic acid (miR-148a) and pomegranate extract (miR-34a) [148–150]. Of particular interest is the approved anticancer drug etoposide, which is a topoisomerase II inhibitor derived from podophyllotoxin and applied for the treatment of breast cancer and lung cancer [151,152]. A p53-dependent upregulation of the tumor suppressor miR-34a was observed from cancer cells upon etoposide treatment [153].

A list of polyphenolic drugs and their effects on non-coding RNAs is given in Table 3.

2.3.2. Terpenoids

The approved terpenoid anticancer drug paclitaxel (taxol, ex *Taxus brevifolia*) stabilizes microtubules and blocks mitosis in cancer cells but it showed no improved activity against MPM as single-compound in a phase II study [154]. However, in combination with carboplatin a 71-years old female peritoneal mesothelioma patient was cured [155]. More recently, nanoparticle albumin-bound paclitaxel in combination with carboplatin exhibited repeated responses in a 76-years old male patient with epitheloid MPM who did not respond to carboplatin/pemetrexed treatment and, thus, this treatment features a suitable therapy for patients who cannot tolerate cisplatin and pemetrexed first-line treatment [156]. It was shown that paclitaxel induced miR-34a expression, which may function as a putative anticancer mode of action of paclitaxel in combination with platinum drugs [157]. Docetaxel, a close analog of paclitaxel, upregulated miR-34a expression in epithelial MPM cells and exhibited excellent cytotoxic properties in fast growing MPM cells [158].

Triterpenes generally feature a very interesting natural product class with strong anticancer potential. The oncomir miR-21 was suppressed by various natural triterpenes such as ursolic acid, cucurbitacin I, and ginsenoside Rh2, the latter compound Rh2 also induced the tumor suppressor miR-148a [159–162]. Another triterpene isolated from *Boswellia* plants and resins (frankincense is usually prepared from

Table 3
Polyphenolic drugs with effects on non-coding RNA tumor suppressors (inducing effects) and oncogenes (suppressing effects) in mesothelioma correlated with cisplatin activity.

Drugs	Tumor suppressors	Oncogenes
EGCG	let-7c, miR-1, miR-7, miR-34a, miR-34b/c, NEAT1	miR-21, miR-210
Genistein	miR-34a, miR-200c	miR-21, HOTAIR
Glyceollins	miR-34a	miR-21
3,6-DHF	miR-34a	miR-21
Quercetin	miR-34a	–
Silibinin	miR-200c	miR-21
Curcumin	miR-7, miR-34a, miR-145, miR-200b/c, miR-203	miR-17–5p, miR-21, HOTAIR, H19, PVT1
CDF	–	miR-21, miR-210
Resveratrol	miR-34a, miR-34c, miR-200c, NEAT1	miR-21, MALAT1
Pterostilbene	miR-200c	–
Emodin	miR-34a, miR-429	miR-210
Magnolol	miR-200c	–
Honokiol	miR-34a	–
Garcinol	miR-200b, miR-200c	miR-21
Glabridin	miR-148a	–
Caffeic acid	miR-148a	–
Pomegranate extract	miR-34a	–
Etoposide	miR-34a	–

the resin of *Boswellia* plants) named AKBA (3-acetyl-11-keto-β-boswellic acid) upregulated miR-34a and miR-200 expression [163,164]. In addition, the triterpene enoxolone isolated from licorice induced miR-200c [145].

The vital natural diterpene retinoic acid (RA, vitamin A) upregulated the tumor suppressors let-7c and miR-223 [165,166]. Delta-tocotrienol is closely related to vitamin E and increased the expression of the tumor suppressor miR-34a [167]. In addition, the fungal sesquiterpene lactone antrocin induced let-7c expression, while the PEGylated monoterpene thymoquinone (ex *Nigella sativa*) upregulated miR-34a [168,169].

A list of terpenoid drugs and their effects on non-coding RNAs is given in Table 4.

2.3.3. Alkaloids

Several alkaloids such as camptothecins (quinoline alkaloids ex *Camptotheca acuminata*) and Vinca alkaloids (indole alkaloids ex *Catharanthus roseus*) are currently applied for the treatment of various cancer diseases and their strong influence and dependence on miRNA expression was summarized recently [170]. The semi-synthetic analog vinorelbine is of particular interest for cancer diseases affecting the lung, and vinorelbine (navelbine) is often off-label applied as a second-line treatment of MPM patients who had suffered from a severe relapse [171]. In addition, vinorelbine exhibited promising results as a combination partner of cisplatin for a first-line chemotherapy [172]. Structurally more simple natural indoles are represented by 3,3′-diindolylmethane (DIM) and indole-3-carbinol (I3C, ex *Brassica* vegetables), which are able to modulate the expression of various relevant non-coding RNAs in tumors [173]. I3C suppressed the oncomirs miR-21 and miR-31 in lung tumors [174]. DIM induced the expression of the tumor suppressors let-7c, miR-34, and miR-200b/c [175–177].

Table 4
Terpenoid drugs with effects on non-coding RNA tumor suppressors (inducing effects) and oncogenes (suppressing effects) in mesothelioma correlated with cisplatin activity.

Drugs	Tumor suppressors	Oncogenes
Paclitaxel	miR-34a	–
Ursolic acid	–	miR-21
Rh2	miR-148a	miR-21
AKBA	miR-34a, miR-200	–
Enoxolone	miR-200c	miR-210
Retinoic acid	let-7c, miR-223	–
Δ-Tocotrienol	miR-34a	–
Antrocin	let-7c	–
PEG-Thymoquinone	miR-34a	–

The topoisomerase I inhibitor camptothecin (ex *Camptotheca acuminata*) and its water-soluble derivatives irinotecan and topotecan represent quinoline alkaloids and are approved for the treatment of various tumor diseases [178]. Interestingly, topotecan upregulated miR-34b expression in cancer cells and, thus, represents a suitable combination partner for cisplatin [179]. The close analog irinotecan was investigated in MPM patients in combination with cisplatin in a phase 2 trial and this combination was well tolerated by the treated MPM patients and exhibited distinct anticancer activity (overall response rate of 40%) [180]. The alkylating tetrahydroisoquinoline trabectedin (Ecteinascidin 743, Yondelis®) was isolated from the Caribbean tunicate *Ecteinascidia turbinata* and is approved for the treatment of soft tissue sarcoma [181]. Trabectedin exhibited promising results from a phase 2 trial with epithelioid MPM patients and from patients with sarcomatoid/biphasic MPM [182,183]. Concerning miRNAs, trabectedin suppressed miR-21 expression probably by regulation of FUS-CHOP in cancer cells [184]. Indeed, the combination of trabectedin with cisplatin exhibited synergistic effects against MPM cells [185]. In addition, the isoquinoline alkaloid berberine (ex *Berberis aristata*) enhanced the activity of cisplatin by suppression of oncogenic miR-21 while the isoquinoline palmatine chloride upregulated the tumor suppressors miR-34a and miR-200c [186,187].

A list of alkaloid drugs and their effects on non-coding RNAs is given in Table 5.

2.3.4. Miscellaneous natural products

Further natural products that don't belong to the compound classes mentioned above modulated miRNAs in cancers. Concerning mesothelioma-relevant miRNAs with influence on cisplatin activity, vitamin C (ascorbate) induced the expression of the tumor suppressor miR-345 [188]. Docosahexaenoic acid (DHA), a potent component of vitamin F (i.e., polyunsaturated fatty acids) from fish oil, suppressed oncogenic miR-21 [189]. Natural organosulfur compounds such as diallyl disulfide (DADS), sulforaphane (SFN) and phenethylisothiocyanate (PEITC) found in garlic, leek and onions induced the expression of various tumor suppressors including let-7c (by PEITC), miR-34a (by DADS), miR-145 (by SFN), miR-200b (by DADS), and miR-200c (by SFN) [190–195].

A list of miscellaneous natural drugs and their effects on non-coding RNAs is given in Table 6.

2.3.5. HDAC inhibitors

The acetylation state of histone proteins controls gene expression, and the acetylation of histones and of other vital proteins (e.g., tubulin) is regulated by histone deacetylases (HDACs) and histone acetyltransferases (HATs) [196]. In particular, HDAC inhibitors have become more and more important for cancer treatment and some compounds were already approved for the treatment of T cell lymphoma (SAHA/

Table 5
Alkaloid drugs with effects on non-coding RNA tumor suppressors (inducing effects) and oncogenes (suppressing effects) in mesothelioma correlated with cisplatin activity.

Drugs	Tumor suppressors	Oncogenes
I3C	–	miR-21, miR-31
DIM	Let-7c, miR-34, miR-200b/c	–
Topotecan	miR-34b	–
Trabectedin	–	miR-21
Berberine	–	miR-21
Palmatine	miR-34a, miR-200c	–

Table 6
Miscellaneous natural drugs with effects on non-coding RNA tumor suppressors (inducing effects) and oncogenes (suppressing effects) in mesothelioma correlated with cisplatin activity.

Drugs	Tumor suppressors	Oncogenes
Vitamin C	miR-345	–
DHA	–	miR-21
DADS	miR-34a, miR-200b	–
SFN	miR-145, miR-200c	–
PEITC	let-7c	–

vorinostat, belinostat, romidepsin) and multiple myeloma (panobinostat) [197]. Sodium butyrate (NaB), the salt of the short fatty acid butyric acid, represents the structurally simplest HDAC inhibitor. NaB was shown to induce the expression of the tumor suppressor miR-145 [198]. The natural HDAC inhibitor trichostatin A (TSA) induced miR-1, miR-7, miR-34a, miR-203, and miR-486 [199–201]. The clinically approved HDAC inhibitor suberoylanilide hydroxamic acid (SAHA, vorinostat) upregulated miR-34b expression [202]. In addition, vorinostat suppressed the expression of the lncRNA HOTAIR [203]. However, there were also reports which disclosed negative effects by treatment with HDAC inhibitors. Sodium phenylbutyrate (NaPBA) suppressed miR-34b/c [204]. SAHA suppressed miR-7, miR-200b and miR-345 [202,205]. Panobinostat, another approved HDAC inhibitor, upregulated oncogenic miR-31 [206].

There is only limited data for HAT inhibitors and the effects of the natural phenolic HAT inhibitor garcinol on the expression of non-coding RNAs are given in Table 3.

A list of HDAC inhibitors and their effects on non-coding RNAs is given in Table 7.

2.3.6. Cisplatin as sensitizer for other approved anticancer drugs

It was observed that cisplatin treatment led to the induction of tumor suppressor miRNAs (let-7c, miR-34a, miR-145, miR-451) and suppression of oncomirs (miR-210) and, thus, cisplatin can potentiate the efficacy of other chemotherapeutic drugs which depend significantly on the regulation of these miRNAs (Fig. 4) [44,61,87,88].

Pemetrexed is an antimetabolite often applied in combination with cisplatin for the first-line treatment of MPM. Upregulation of the tumor suppressor miR-145 sensitized MPM cells to pemetrexed [86]. As shown before, cisplatin induced miR-145 expression in bladder cancer cells [87,88]. It is conceivable that the relatively high activity of the combination of cisplatin with pemetrexed in MPM patients is in parts due to miR-145 regulation.

As already mentioned above, Vinca alkaloids have shown promising activity against mesothelioma. Vincristine- and vinorelbine-resistant cancer cells revealed upregulated miR-210, which is an oncomir suppressed by cisplatin [207,208]. Thus, miR-210 suppression by cisplatin can be one reason for the distinct activity of the combination of cisplatin with vinorelbine in certain mesothelioma patients [172].

The small molecule tyrosine kinase inhibitor sorafenib showed promising activity from a phase 2 trial with malignant mesothelioma patients who were pre-treated with platinum drugs [209]. Cancer cells resistant to sorafenib exhibited reduced let-7c and miR-34a expression when compared with parental cells and combination of sorafenib with cisplatin, which was able to induce both let-7c and miR-34a, appears a promising therapy option [210].

Table 7
HDAC inhibitors with effects on non-coding RNA tumor suppressors (inducing effects) and oncogenes (suppressing effects) in mesothelioma correlated with cisplatin activity.

Drugs	Tumor suppressors	Oncogenes
NaB	miR-145	–
TSA	miR-1, miR-7, miR-34a, miR-203, miR-486	–
SAHA	miR-34b	HOTAIR

2.3.7. The role of p53 and miR-34a for cisplatin activity

DNA-damage induced by the reaction of cisplatin with nucleobases of the cellular DNA often leads to p53-activation and apoptosis induction [211]. The tumor suppressor p53 is an instable protein which is activated, i.e., phosphorylated, by Ataxia telangiectasia mutated protein (ATM). Activated p53 stimulates the E3 ubiquitin ligase Mdm2 and leads to overexpression pf PTEN [212]. The transcription activity of p53 is also regulated by acetylation and SIRT1-mediated deacetylation of p53 reduced its transcriptional activity [213]. It was shown that activated p53 was involved in gene transcription of miR-34a as a consequence of DNA damage (Fig. 5) [214,215]. The promoter region of miR-34a has a p53-binding element, however, hyper-methylation of a CpG island in the promoter region silences p53-dependent transcription [213,215]. The transcript of miR-34a is initially a long hairpin RNA molecule (Pri-miR34a) that is processed by DROSHA (a human RNase III) to Pre-miRNA34a, exported from the nucleus to the cytosol where it is processed by DICER (another human RNase III) to a double-stranded 22–23 nucleotide RNA molecule [215]. One strand of mature miR-34a is finally incorporated in RISC (RNA-induced silencing complex) [215]. Most targets of miR-34a include anti-apoptotic proteins (Bcl-2), proteins responsible for G1/S transition (c-MYC, E2F, CDK2, CDK6) and for invasion (c-MET), and signaling pathways (Notch, AR) [214,215]. Inhibition of target genes occurs by binding of the seed-sequence of miR-34a, which is a sequence of 7 nucleotides located at the 5′-end, with the target mRNA via a complementary DNA sequence of the 3′-UTR of this target mRNA [216]. Further interactions can occur between the target mRNA and nucleotides of the middle and 5′-end of miRNA-34a [215]. Upregulation of miR-34a expression often sensitized cancer cells to cisplatin treatment [215]. As a suitable therapeutic option, a liposomal formulation of a miR-34a mimic called MRX34 has entered clinical phase 1 studies [217]. Further strategies to formulate miR-34a include CD44-targeting systems (hyaluronic acid/protamine sulfate interpolyelectrolyte complexes) and other tumor-targeting bifunctional peptides combined with β-cyclodextrin-polyethylimine [218,219]. Given the eminent role of miR-34a concerning the suppression of mesothelioma an application of suitable therapeutic miR-34a formulations alone or in combination with cisplatin or carboplatin seems promising. As already mentioned above, minicells loaded with miR-16 mimic miRNA already underwent a phase 1 trial with MPM patients and revealed promising results [29].

2.4. Carboplatin, non-coding RNAs and mesothelioma

As already mentioned above, cancer treatment with carboplatin represents a less toxic alternative to cisplatin treatment. Carboplatin in combination with pemetrexed revealed similar results (and even slightly improved survival) as the widely applied first-line MPM therapy cisplatin plus pemetrexed, and the carboplatin plus pemetrexed chemotherapy was well tolerated [220]. Due to the very similar modes of action of cisplatin and carboplatin most of the already described non-coding RNAs and non-coding RNA modulating molecules involved in cisplatin activity likely play a significant role for carboplatin efficacy in mesothelioma as well. For instance, upregulation of oncogenic miR-31 induced resistance of MPM cells to carboplatin and cisplatin [43]. Replacement of cisplatin by carboplatin is indicated for certain vulnerable patients in order to avoid nephrotoxicity, which is very common upon cisplatin treatment, however, myelotoxicity/bone marrow suppression may occur during carboplatin therapy [34].

3. Conclusions

Approved anticancer Pt(II) complexes modulated the non-coding RNA profile of mesothelioma. Vice versa, several non-coding RNAs

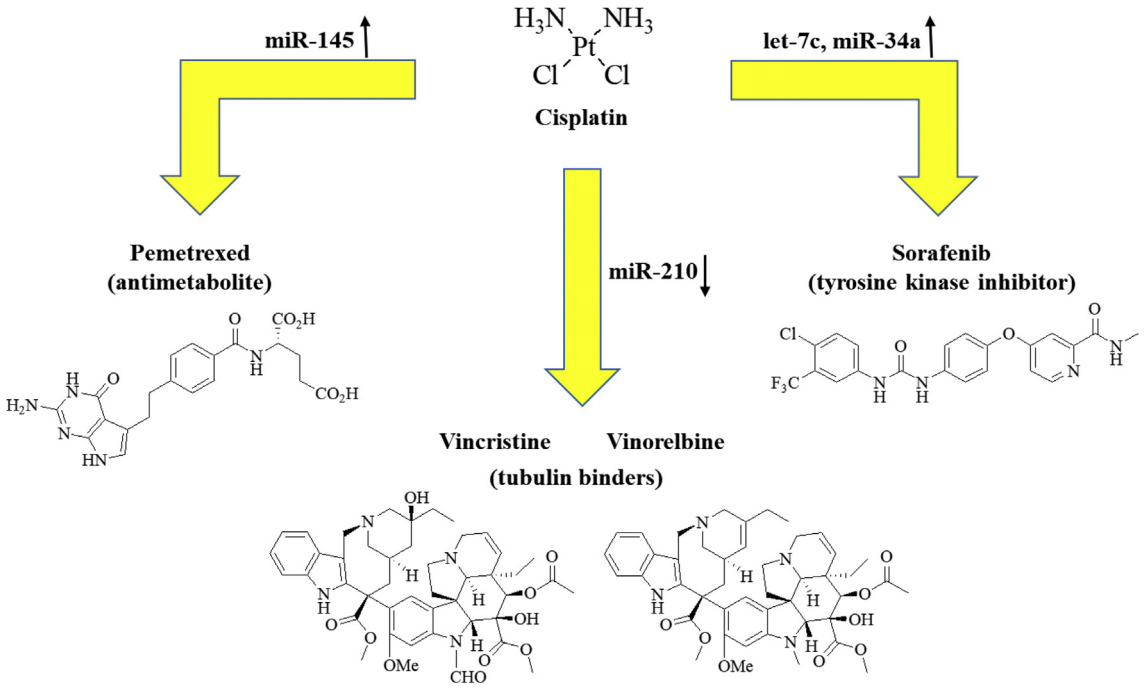


Fig. 4. Possible activity boost of approved anticancer drugs by cisplatin-mediated miRNA modulation.

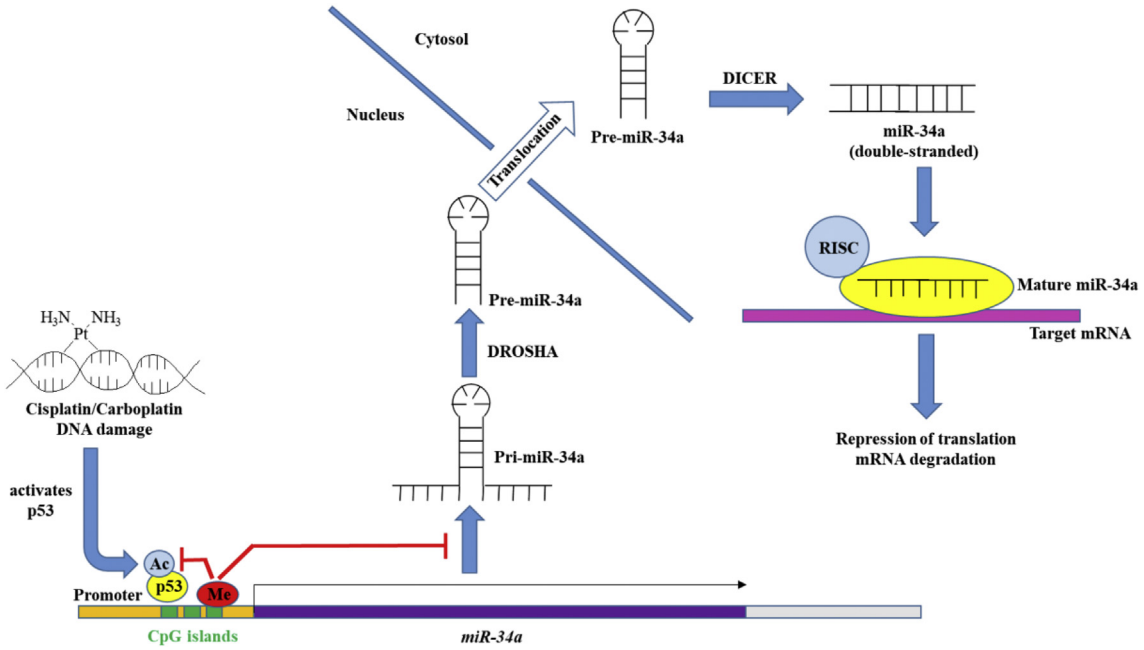


Fig. 5. Activation of p53 and miR-34a induction by platinum complexes.

were identified that influenced platinum activity in mesothelioma either positively or negatively. Platinum resistance as well as side-effects by platinum complexes are regulated by non-coding RNAs. An exact knowledge of the interactions between anticancer active approved platinum complexes and non-coding RNAs is of high importance. In addition, the interplay between platinum complexes and the key tumor suppressors p53 and miR-34a is of relevance. A better understanding of the roles of non-coding RNAs for the activity of platinum complexes is expected to lead to improved anticancer therapy regimens of mesothelioma diseases based on platinum compounds such as cisplatin and carboplatin, and to better survival rates and prognoses due to the circumvention of platinum resistance and the improvement of life quality of affected mesothelioma patients.

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