Review

Cisplatin resistance: Preclinical findings and clinical implications

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A B S T R A C T

Cisplatin is used for the treatment of many types of solid cancers. While testicular cancers respond remarkably well to cisplatin, the therapeutic efficacy of cisplatin for other solid cancers is limited because of intrinsic or acquired drug resistance. Our understanding about the mechanisms underlying cisplatin resistance has largely arisen from studies carried out with cancer cell lines *in vitro*. The process of cisplatin resistance appears to be multifactorial and includes changes in drug transport leading to decreased drug accumulation, increased drug detoxification, changes in DNA repair and damage bypass and/or alterations in the apoptotic cell death pathways. Translation of these preclinical findings to the clinic is emerging, but still scarce. The present review describes and discusses the clinical relevance of *in vitro* models by comparing the preclinical findings to data obtained in clinical studies.

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Contents

1. Introduction

Cisplatin (cis-diammine-dichloroplatinum (II)) is one of the most widely used and effective anticancer agents. It plays a major role in the treatment of a variety of cancers, including testicular, bladder, ovarian, head and neck, cervical, lung and colorectal cancer [1,2]. Cisplatin works by binding to DNA leading to different types of DNA

lesions [3]. The most frequently observed lesions produced by cisplatin are intrastrand DNA adducts between adjacent guanines (65% of all lesions) or adducts between guanine and adenine (25%). Interstrand crosslinks between two guanines on the opposite strands of DNA account for less than 5% of all cisplatin-induced lesions. Although there is still some controversy whether intra- or interstrand crosslinks are the critical lesions responsible for cisplatin toxicity [4], it has been proposed that cisplatin damage causes G2 arrest in the cell cycle before apoptosis is triggered [5,6].

The efficacy of cisplatin in cancer treatment is limited due to resistance, either intrinsic (e.g. as observed in patients with colorectal, lung and prostate cancer) or acquired following cisplatin chemotherapy (as often seen in patients with ovarian cancer). The mechanism of cisplatin resistance has been studied in several types of cisplatin-resistant cell lines and appears to be multifactorial. It has been shown that cancer cells can develop cisplatin resistance through changes in (1) drug transport leading to reduced intracellular cisplatin accumulation, (2) an enhanced drug detoxification system due to elevated levels of intracellular scavengers such as glutathione and/or metallothioneins, (3) changes in DNA repair involving increased nucleotide excision repair, interstrand crosslink repair or loss of mismatch repair, (4) changes in DNA damage tolerance mechanisms and finally (5) changes in the apoptotic cell death pathways [7,8] (Fig. 1). The findings obtained in preclinical studies have provided valuable information about resistance factors, which could be the basis for strategies used to overcome this phenotype in the clinic.

2. Intracellular drug accumulation and cisplatin resistance

2.1. Cellular uptake of cisplatin

For many tumor cell lines with acquired resistance to cisplatin a reduced drug accumulation in comparison to the parental cell line has been observed [9,10]. These findings suggest changes in the cisplatin transport system resulting in a decreased uptake and/or an increased efflux as a mechanism for drug resistance. In addition to passive diffusion, a role for plasma membrane transporters has been suggested. Copper transporter 1 (Ctr1) that controls intracellular copper homeostasis was shown to be involved in the uptake of cisplatin [11–13]. The importance of Ctr1 in cisplatin sensitive and resistant cell lines has been investigated and a reduced expression of Ctr1 in a cisplatin-resistant lung cancer cell line has been reported [14]. However, in a study using oral squamous carcinoma cell lines the expression of Ctr1 was the same in sensitive and resistant cell lines [15]. Thus, the relevance of Ctr1 for cisplatin resistance seems to be specific for the type of tumor cell. No data as to Ctr1 expression in solid tumors and its relation to cisplatin resistance have been reported to date (Table 1).

2.2. Inactivation by thiol-containing proteins

Cisplatin resistance can arise as a result of increased inactivation of the drug by intracellular thiol-containing molecules such as glutathione and metallothionein. Glutathione is a protective tri-peptide that, besides its role in maintaining the redox environment of the cells, scavenges free radicals and therefore protects cells from xenobiotic substances. In a reaction catalyzed by glutathione-S-transferase (GST) cisplatin can be conjugated with glutathione resulting in the prevention of its binding to other cellular molecules such as DNA. The role of the glutathione system for cisplatin resistance has been studied extensively in both cell lines and cancer tissues. An increased concentration of glutathione or GST could be correlated with cisplatin resistance in ovarian, cervical, lung, embryonal and bladder cancer cell lines [10,16–18] although this has not been observed in all cases [19,20]. Similarly, attempts to correlate the expression of glutathione or GST with the response rate to cisplatin in cancer patients showed inconsistent findings. While in some studies it was found that in patients with head and neck cancer or non-small cell lung carcinoma glutathione or GST expression may be associated with
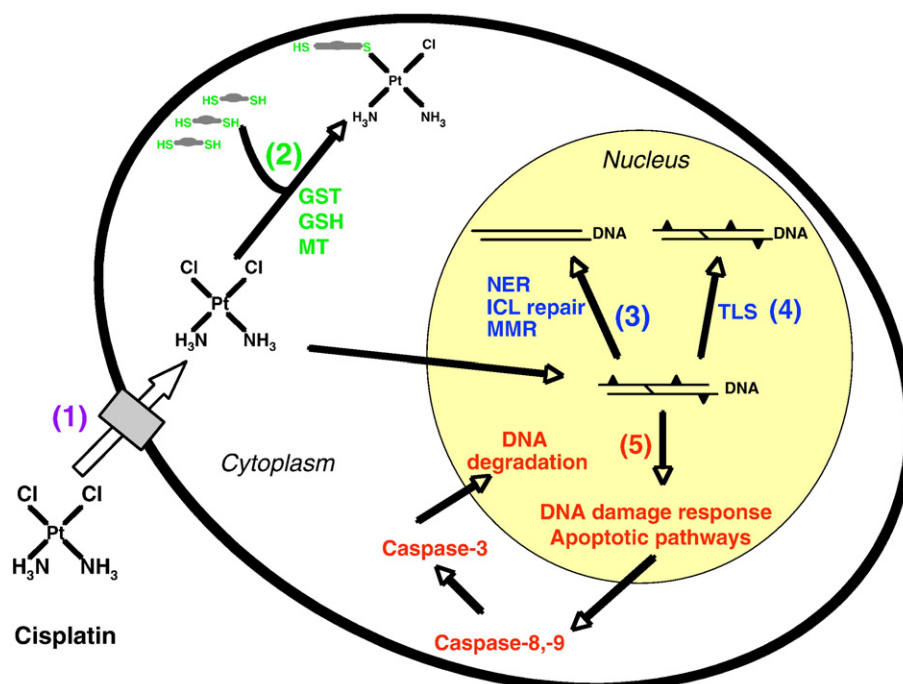
Fig. 1. Mechanisms of resistance towards cisplatin. (1) Changes in efflux/uptake: decreased expression of Ctr1 will lead to a reduced accumulation of cisplatin in the cell. (2) Detoxification of cisplatin in the cytoplasm by the glutathione system or metallothioneins: increased levels of glutathione (GSH), glutathione-S-transferase (GST) or metallothioneins (MT) result in increased detoxification of the drug. (3) Alterations in DNA repair: increased removal of cisplatin-induced lesions from the DNA due to increased nucleotide excision repair (NER) or increased interstrand crosslink repair (ICL repair). Reduced mismatch repair (MMR) can lead to futile repair triggering apoptosis. (4) Increased expression of translesion synthesis (TLS) polymerases enables cells to tolerate unrepaired cisplatin lesions (5) Alterations in the apoptosis pathway: reduced apoptosis induction by cisplatin due to decreased expression or loss of pro-apoptotic factors. Conversely increased expression of anti-apoptotic factors can result in drug resistance.

Table 1
Molecular mechanisms of cisplatin resistance: preclinical findings and clinical evidence.

Molecular mechanism	Preclinical evidence	Clinical evidence
Intracellular cisplatin accumulation		
Decreased uptake/ increased efflux	Observed in resistant cancer cell lines	No data reported
Increased glutathione/GST levels	Observed in resistant cancer cell lines	Conflicting results
Increased metallothionein levels	Observed in resistant cancer cell lines	Conflicting results
DNA repair		
Nucleotide excision repair (NER)	High levels of ERCC1 in resistant cancer cells	High levels of ERCC1 in less responsive tumors
ICL repair	Decreased in sensitive testis tumor cell lines	Increased in cells of relapsed ovarian cancer
Translesion synthesis (TLS)	Deficiency in polymerase activity associated with sensitivity	Correlation with clinical resistance in some tumors
Mismatch repair (MMR)	Deficiency in some resistant cancer cell lines	Deficiency in some tumors with acquired resistance
DNA damage response		
SAPK/JNK	Transient activation in resistant cancer cell lines	No data available
Bcl-2, Bcl-xL	Overexpression in resistant cancer cell lines	Correlation with clinical resistance
XIAP	Enhanced expression associated with resistance	Conflicting data
XAF1	No data available	High levels correlated with better prognosis
p53	Inactivation associated with resistance	Good response in p53 wild-type tumors

cisplatin resistance and poor clinical outcome [21–23], no significant relationship of GST expression with either response rate or survival after cisplatin treatment has been observed in patients with cervical, ovarian carcinoma or non-small cell lung cancer [24–26] (Table 1).

Metallothioneins (MT) belong to a family of low molecular weight, thiol-rich proteins that play a role in metal homeostasis and detoxification. MTs can bind cisplatin leading to drug inactivation. Several studies have investigated the importance of MT expression for cisplatin resistance in cell lines derived from cancer of the prostate, lung, ovary and cervix and suggested a correlation between the increased expression of MT and the resistance to cisplatin [10,27–29]. Similarly, an association between MT expression and cisplatin resistance has been investigated in cancer tissue, however with conflicting results. While MT overexpression has been associated with clinical resistance to cisplatin in bladder cancer and cancer of the urinary tract [30,31], no relation between MT expression and response to cisplatin was observed in germ cell tumors or ovarian cancer [32,33]. However, another study pointed out that nuclear expression of MTs is specific for ovarian cancers of poor outcome while no relationship could be demonstrated between cytoplasmic expression of MTs and clinical variables [29]. Altogether these studies indicate that nuclear MT expression can contribute to cisplatin resistance in some solid tumors, but evidence is weak and, therefore, MTs are likely of minor importance for cisplatin resistance of tumors (Table 1).

2.3. Cisplatin lesion binding proteins

All cisplatin-induced lesions result in DNA distortions, which can be recognized by a number of proteins, including the MutSα protein of the mismatch repair system [34], members of the high mobility group HMG1/2 family [35], histone H1 [36], the RNA pol-I binding factor hUBF [37] and the TATA-binding protein TBP [38]. It is assumed that binding of these factors inhibits or limits the repair of cisplatin damage. However, with the exception of MutSα (see below) the effect of these binding proteins on cisplatin resistance has only been assessed *in vitro* and no information is available on their impact on resistance in clinical samples.

3. DNA repair and cisplatin resistance

3.1. Nucleotide excision repair and interstrand crosslink repair

The relevance of DNA repair for cisplatin resistance has been studied for many years. Some investigations indicate a possible role of repair for intrinsic and acquired resistance while others fail to show a contribution of DNA damage removal for the acquired resistance phenotype. A major reason for the uncertainty of the repair pathways involved is presumably the absence of knowledge as to the critical type of pre-toxic lesion induced by cisplatin. Thus, in most of the studies total DNA platination was compared in resistant and sensitive cell lines and in tumors with clinical outcome. If interstrand DNA crosslinks (<5% of total platination) are a major contributor for cell death upon cisplatin, alterations in its repair level would not be detected by the platination assays.

Many tumor cell lines with acquired cisplatin resistance show an increased capacity for removal of cisplatin-induced DNA lesions in comparison with their cisplatin sensitive counterparts. In A2780 ovarian cancer cell lines increased platination removal was found to be associated with increased resistance [39–41]. However, the increase in lesion removal did not correlate with the degree of acquired resistance in this model system. Similarly, colon carcinoma cell lines with acquired cisplatin resistance showed a higher extent of removal of DNA platination compared to the parental cells, but the decrease in platination levels was not proportional to resistance [42]. In contrast, no enhanced removal of cisplatin-damaged DNA has been observed in other model systems of acquired cisplatin resistance, suggesting that cells did not become resistant to cisplatin by increasing their DNA repair capacity [43–45]. However, in tumor cells exhibiting intrinsic cisplatin sensitivity a correlation between DNA repair capacity and cisplatin response has been reported. Cisplatin sensitive testis tumor cells were found to have a reduced capacity for removing cisplatin damage compared to cisplatin-resistant bladder cancer cells [46], indicating that intrinsic suscepti-bility to cisplatin might be related to the repair capacity.

Cisplatin-induced DNA damage is mainly removed by nucleotide excision repair (NER), the main DNA repair pathway dealing with bulky helix-distorting lesions such as UV-induced cyclobutane pyrimidine dimers and 6-4 photoproducts and DNA lesions induced by many chemotherapeutic drugs [47–49]. NER involves recognition of the damage and incision on both sides of the lesion, followed by DNA synthesis to replace the excised fragment. The core incision reaction requires the protein factors XPA, RPA, XPC-HR23B, TFIIH, ERCC1–XPF and XPG [50]. Using an *in vitro* NER assay it was shown that the reduced repair capacity observed in cisplatin sensitive testis tumor cell lines is due to reduced NER compared to extracts from resistant bladder cancer cells [51]. Inversely, extracts from A2780 ovarian cancer cells with acquired cisplatin resistance exhibited a higher NER capacity compared to their cisplatin sensitive parental cells, suggesting that resistance is due to enhanced NER [52]. However, the increase in repair (2 to 3 fold) did not correlate with the degree of acquired resistance (up to 200 fold) in this model system. Cells selected for cisplatin resistance by continuous cultiva-tion in the presence of the drug often exhibit extreme levels of resistance such as 50 to 200 fold. In these model systems the phenotype of acquired resistance is therefore most likely not simply related to one factor since multiple changes have been shown to occur during selection including enhanced NER.

Conclusive evidence for functionally increased NER in cisplatin-resistant cancers has not yet been presented. A major difficulty is the lack of methods that easily and reliably measure NER activity in tissue

samples. For example, assays measuring the NER capacity in protein extracts typically have significant inherent variability, even when extracts are prepared from the homogenous material available from cell lines. In a pilot study using protein extracts from biopsies of human ovarian carcinoma Jones and co-workers found that the NER capacity varied significantly by as much as ten-fold [53]. This could be due to either inter-individual variations or to technical problems to obtain active extracts from tissue material. Therefore, as measuring NER capacity in tissue samples entails challenges, a different approach is to assess NER factors via mRNA or protein levels and attempt to correlate these with cellular resistance to cisplatin or response to chemotherapy. In these investigations special emphasis was given to ERCC1, the first human DNA repair gene cloned [54]. ERCC1 associates with its partner xeroderma pigmentosum protein F (XPF) to form a structure-specific endonuclease that acts by making a 5′ incision relative to the platination DNA damage [55,56]. In preclinical studies using cisplatin-resistant cell lines that were derived from various types of tumors the resistance phenotype was postulated to correlate with ERCC1 expression [57–59]. Conversely, down-regulation of ERCC1–XPF by siRNA sensitized prostate cancer cells and bladder cancer cells to cisplatin [60,173]. This sensitizing effect has also been observed in cells derived from non-small cell lung cancer, ovarian cancer and breast cancer [61].

In cancer tissues ERCC1 mRNA or protein levels showed an inverse correlation with the response to platinum therapy or overall survival. In gastric carcinoma, elevated levels of ERCC1 mRNA were suggested to be associated with cisplatin resistance [59]. In bladder, colorectal, head and neck, esophageal and non-small cell lung cancer ERCC1 expression negatively contributes to the clinical outcome in patients treated with cisplatin-based chemotherapy [62–67]. Similarly, ovarian cancer tissues from patients whose tumors were resistant to combination therapy with cisplatin had higher ERCC1 mRNA levels as compared to tumor tissues from patients who responded to therapy [68–70]. Based on these findings one might conclude that many, if not most, cisplatin-resistant tumors have an enhanced capacity to repair cisplatin-induced lesions due to increased levels of NER proteins such as ERCC1. However, with functional NER assays for tissue material still missing, it remains speculative whether an altered ERCC1–XPF level has an impact on NER in the tumor tissue. Therefore, the question about the contribution of enhanced NER for cisplatin resistance in cancers remains to be solved. In addition, there is evidence that besides its essential role in NER, ERCC1–XPF participates in certain homologous recombination pathways and facilitates DNA double-strand break repair in eukaryotic cells [71–73]. An altered level of ERCC1–XPF in cancer tissue could therefore cause changes in functions distinct from NER. It should be noted that while the lack of ERCC1 is undoubtedly related to cisplatin sensitivity, which is observed both in cell culture experiments and in the clinic, over-expression of ERCC1 does not necessarily increase resistance. Indeed, transfection of ERCC1 caused sensitization of hamster cells to crosslinking agents [74]. This is likely due to an imbalance in repair pathways as demonstrated for other repair proteins involved in complex repair pathways [75]. In view of the correlation between ERCC1 expression and clinical outcome repeatedly reported for different tumors, we propose to use ERCC1 protein expression as a predictor of response to platinum-based chemotherapy in clinical settings (Table 1).

Besides intrastrand adducts, cisplatin induces interstrand cross-links (ICLs), which are removed by ICL repair, a process not understood completely [76]. Biochemical and cell biological data implicate that ERCC1–XPF is also involved in ICL repair [55,72,77]. Therefore, the increased levels of ERCC1, which have been observed in various human cancer tissues, might result in an enhanced repair of ICLs, resulting in cisplatin resistance. The hypothesis that ERCC1 contributes to ICL repair in tumors is supported by the finding that cisplatin sensitive testis tumor cell lines have a reduced level of ICL

repair, which is due to low levels of ERCC1 and XPF proteins (Usanova et al., submitted). While in testis tumor cells ICL repair is impaired, in ovarian cancer cell lines acquired resistance to cisplatin is associated with increased gene-specific repair of ICLs [78]. This seems also to be true for ovarian cancer tissue, as in paired tumor samples obtained prior to treatment and at relapse following platinum chemotherapy increased repair of cisplatin ICLs in cells of relapsed ovarian cancer was observed [79]. Thus, increased ICL repair appears clearly to contribute to cisplatin resistance in cancers (Table 1).

3.2. Translesion synthesis (TLS)

Although cisplatin damage is removed by NER and ICL repair, some lesions may remain. A mechanism by which cells can tolerate unrepaired DNA lesions is translesion synthesis (TLS), which is carried out by a group of specialized DNA polymerases. TLS polymerases are capable of bypassing unrepaired DNA lesions and have been implicated in tolerance of different types of DNA damage. In mammalian cells these TLS polymerases are pol η (POLH), pol ι (POLI), pol κ (POLK), REV1 and pol ζ (REV3 and REV7), each of which has different substrate specificity. Depending on the type of damage, different combinations of TLS polymerases act in concert to bypass lesions in mammalian cells [80]. For cisplatin, there is evidence that pol η and pol ζ are involved in bypass of cisplatin-GG adducts [80,81]. Using purified enzyme it was reported that pol κ is unable to bypass a cisplatin-GG intrastrand adduct in an in vitro assay [82]. However, in vivo TLS assays implicated pol κ in combination with pol η for TLS across cisplatin GpG intrastrand adducts [80]. Even for pol ß, a member of the mammalian family X DNA polymerases, which are mainly involved in DNA repair, bypass of cisplatin adducts has been observed in vitro [83].

The importance of TLS in the tolerance towards cisplatin has been shown in cell lines deficient in TLS polymerase activity. Thus, deficiency of pol η activity in human cell lines resulted in cisplatin sensitivity, which was associated with increased activation of the DNA damage response [84,85]. In another study pol η deficient cells were more sensitive to cisplatin, carboplatin and oxaliplatin compared to the same cells complemented with the polymerase, again indicating a requirement of pol η for tolerance to platinum drugs [86]. Similarly, mouse embryonic fibroblasts deficient in pol ζ showed increased sensitivity towards crosslinking agents [87,88]. Overexpression of REV3, the catalytic subunit of pol ζ, conferred resistance towards cisplatin in glioma cells [89], while down-regulation of REV3 expression rendered human fibroblasts and colon carcinoma cells more sensitive towards cisplatin [90,91]. In A2780 ovarian cancer cells an association between the acquired cisplatin resistance and an increase in DNA synthesis past platinum adducts has been observed [92]. The pol ß inhibitor masticadononic acid affected TLS synthesis across cisplatin adducts and sensitized cisplatin-resistant A2780 cells, suggesting a contribution of pol ß mediated TLS for the development of platinum resistance [93]. However, similar to NER (Section 3.1) the increase in TLS did not correlate with the degree of acquired resistance [92]. This supports the hypothesis that several factors can determine acquired cisplatin resistance of ovarian cancer cell lines, one of them being TLS.

Expression levels of specialized DNA polymerases were determined in tumor samples from a diverse range of tissues to investigate for an involvement of TLS polymerases in clinical cisplatin resistance. In lung cancer patients who were treated with platinum-based chemotherapy an inverse correlation was found between pol η levels and patient survival time [94]. In glioma tissue expression of REV3 was significantly upregulated and correlated with tumor grade [89]. Comparing the expression pattern of DNA polymerases in a range of matched normal and tumor tissues provided evidence for the overexpression of specialized DNA polymerases in tumor tissue [95]. However, other data show down-regulation of DNA polymerases κ, ι,

η and ζ [96]. Altogether the data indicate a role of TLS polymerases for cisplatin resistance, which may, however, depend on the type of tumor (Table 1). Thus, it would be worth investigating whether the expression levels of specific TLS polymerases, notably polymerases η and ζ, might be used as a predictive marker for the efficacy of platinum therapy in the clinic.

3.3. DNA mismatch repair (MMR)

Mismatch repair (MMR) is the major pathway that corrects single base mispairs or looped intermediates which arise during DNA replication or as a result of damage to DNA. The MMR process consists of recognition of the mismatch, identification and excision of the mispairs or looped intermediates and re-synthesis of the excised strand [97]. An involvement of MMR in cisplatin-triggered responses and cell death was first proposed on the basis of the finding that the mismatch repair complex MutSα (which is a heterodimer containing MSH2 and MSH6) binds to cisplatin DNA adducts *in vitro* [34,98]. Theoretically, binding of MutSα to cisplatin adducts could start the MMR process by recruiting MutLα (consisting of MLH1 and PMS2). The attempt to remove cisplatin lesions is thought to result in lethal intermediates, which are proposed to set off a futile MMR cycle similar to what has been reported for methylating agents [99]. Alternatively, the MMR complex bound to DNA is suggested to cause a direct activation of the DNA damage response (DDR). A third model is based on the finding of replication bypass of 1,2-intrastrand crosslinks by TLS polymerases [80,81]. Since TLS polymerases are error prone causing mis-incorporation of bases, mismatches will be generated that are recognized by the MutSα complex. This in turn causes a futile repair cycle that triggers DDR. New data suggest that mitochondrial pro-death signalling involving cytochrome c and caspases-9 and -3 is required for the execution of MMR protein-mediated induction of cell death by cisplatin [100].

Futile repair or MMR-triggered DDR is supposed to be a toxic event because MMR deficient cell lines were found to be more tolerant to cisplatin [101]. For example, both MLH1 deficient colorectal cancer cells and MSH2 deficient endometrial adenocarcinoma cells were more resistant to cisplatin, which was explained on the hypothesis that in the absence of MMR cisplatin lesions are not processed into lethal intermediates [102]. Similarly, human embryonic kidney 293T cells became more resistant towards cisplatin when the MMR status of the cells was switched from proficient to deficient [103]. However, investigations in ovarian carcinoma cell lines with acquired cisplatin resistance revealed that defective MMR is only a minor contributor for the resistance phenotype [104]. Even more, no evidence for a direct involvement of MMR deficiency in cisplatin resistance has been found in A2780 ovarian cancer cells and cisplatin-resistant sublines CP1A–12A [105]. The sublines, which varied in resistance from 1.5 to 2.5 fold, were fully MMR proficient as shown using an *in vitro* assay. Similarly, a subline of A2780 cells, which was generated through chronic exposure to increasing concentrations of cisplatin, has been shown to be MMR defective due to the lack of MLH1 expression because of promoter hypermethylation [106]. This CP70 subline is about 10-fold more resistant to cisplatin compared to the parental line, which is in contrast to a 1.5–2-fold difference in survival observed in other matched MMR proficient and deficient tumor cell systems [107]. It should be noted that, importantly, CP70 cells are unable to upregulate p21 following DNA damage indicating that p53 transactivation activity is impaired. Therefore, it is likely that p53 mutation might cause the high level of resistance of these cells. This points to the need of strictly isogenic cell system, such as HEK 293T cells, in which MLH1 controlled by an inducible promoter was stably transfected. The sensitivity difference to cisplatin between MLH1 expressing and non-expressing cells was 2-fold [107]. In line with this are data obtained with mouse embryonic stem (ES) cells lacking MSH2, which revealed a similar sensitivity to cisplatin as MSH2 proficient wild-type cells.

Moreover, restoring MSH2 activity by gene transfer did not sensitize the cells to cisplatin, demonstrating that in ES cells MMR is not involved in cisplatin resistance [108]. Overall, the data indicate that MMR is not a major contributor to cisplatin-induced cell death and that caution is required if non-isogenic cancer cell lines are compared.

The clinical relevance of loss of MMR for cisplatin chemotherapy has been investigated in a number of clinical studies. In patients with ovarian cancer clinical findings indicate a possible role of MMR deficiency in acquired cisplatin resistance, whereas no correlation was found with intrinsic resistance to the drug [109,110]. Loss of MMR in ovarian cancer has been shown to be the result of hypermethylation of the hMLH1 gene [106,110]. However, as shown in ovarian cancer tissues, hundreds of genes can become aberrantly methylated in advanced disease [111]. Therefore, hMLH1 gene methylation could be a consequence of global methylation that went on during tumor progression. For testicular germ cell tumors (TGCT) a correlation between decreased immunostaining of hMLH1 and hMSH2 in tumors and cisplatin treatment failure was reported, and it was concluded that MMR deficiency is associated with chemotherapy resistance in TGCT [112]. In another study involving 162 cases of TGCT it was also observed that a low degree of MLH1 immunostaining was related to a shorter time to tumor recurrence. In addition, in these testis cancer specimens a high degree of microsatellite instability (MSI), which results from inactivating mutations in the MMR system, was associated with clinical relapse [113]. Based on these findings it was concluded that platinum chemotherapy does not appear to be very effective in tumors with MMR deficiency [113]. Taken together, even though some cell culture studies suggest that MMR impacts cisplatin-induced cell death, it is most likely only a minor factor contributing to the development of cisplatin resistance in the clinic (Table 1).

4. DNA damage response and apoptosis pathways in cisplatin resistance

Cisplatin kills cancer cells by inducing apoptosis [5]. The pathways leading to cisplatin-induced apoptosis are subject of considerable current interest, hence yet not fully understood. Cisplatin-induced apoptosis may be triggered through the extrinsic death receptor pathway or the intrinsic mitochondrial pathway, mediated through various proteins such as the JNK signalling cascade, p53 and anti- or pro-apoptotic members of the Bcl-2 family proteins [114–116]. Resistance to cisplatin might occur through decreased expression or loss of pro-apoptotic factors or increased expression of anti-apoptotic proteins [117]. These mechanisms will be discussed.

4.1. p53 and cisplatin resistance

The tumor suppressor protein p53 plays an important role in the apoptotic pathway in the response of cancer cells to chemotherapeutic drugs. Several investigations have studied the influence of the p53 status for cisplatin resistance in cancer-derived cell lines, however with contradictory results. In a survey comparing cisplatin response in breast, lung, colon, kidney, ovarian, leukaemia, melanoma and prostate cancer cell lines it was shown that p53 mutated cell lines were more resistant to cisplatin compared to p53 wild-type cell lines [104,118]. Similarly, p53 inactivation resulted in cisplatin resistance in glioma cell lines [119]. Using p53 siRNA we found that down-regulation of p53 resulted in increased cisplatin resistance in testis tumor cell lines (own unpublished observations). It should be noted that p53 upregulates the death receptor Fas/CD95/Apo-1 in TGCT cell lines, which drives the cells effectively into apoptosis [120]. Our own results show a significant induction of FasR only in cisplatin sensitive testicular cancer cells but not in resistant bladder cancer cells which have no functional p53. p53-driven transcriptional activation of Fas/CD95 pathway is, in our opinion, one of the main reasons for the sensitivity of testis tumor cell lines and other p53 positive tumor cells

to cisplatin. It was also shown that cisplatin-resistant metastatic colon cancer cells lacking a functional p53 protein not only had reduced levels of FasR but also of Apaf-1, a major protein involved in the formation of the apoptosome complex, driving the mitochondrial intrinsic pathway [121]. In addition, knock-down of Apaf-1 in lung adenocarcinoma A-549 and osteosarcoma U2-05 cells resulted in reduced cisplatin-induced apoptosis [122]. In contrast, no correlation was found between cisplatin resistance and p53 status in a panel of human testis tumor cell lines [123,124]. A similar lack of correlation between cisplatin resistance and p53 status was observed in ovarian cancer cell lines [123,124] indicating that in these cases the susceptibility to apoptosis induction following cisplatin is not related to the p53 status.

In contrast to *in vitro* observations, data obtained with tumor samples showed that the p53 status can be a strong predictor for the response to platinum-based chemotherapy. Ovarian cancer patients with wild-type p53 tumors have a good chance to respond, while patients with tumors harbouring p53 mutations experience a lower chance to achieve a complete response following cisplatin therapy [125]. In another study mutant p53 was associated with histological grading in cancer tissue of ovarian cancer patients, and patients with p53 wild-type tumors responded significantly better to cisplatin-based therapy [126]. TGCT show an exquisite sensitivity towards cisplatin therapy and 70–80% of the patients can be cured even when the tumor has metastasized [127]. In contrast to most other types of cancer, almost all TGCT are characterized by wild-type p53 [128] which, together with the ability to activate p53-triggered apoptotic pathways, might explain the extreme sensitivity of these tumors to cisplatin. In support of this, TGCT from patients who failed cisplatin chemotherapy could be linked to a mutation in p53 [129]. Collectively the data strongly suggest a role for p53 in mediating cisplatin resistance in TGCT and other p53 positive tumors. Altogether, p53 wild-type cancers appear to respond better to cisplatin treatment.

4.2. Activation of signal transduction pathways

Even though the exact mechanism of cisplatin signalling is poorly understood, the cellular response to cisplatin is known to involve the activation of the MAP kinases SAPK/JNK (stress-activated protein kinases/c-Jun-N-terminal kinases) and p38 kinases, which is accompanied by upregulation of AP-1 and FasL leading to the induction of caspase activity and apoptosis [117,130]. In preclinical studies comparing parental HeLa or ovarian 2008 cells with the respective resistant sublines it has been shown that cisplatin sensitivity is dependent on a sustained activation of SAPK/JNK and p38 kinase followed by a sustained activation of AP-1 and FasL, while only a transient activation of the SAPK/JNK pathway together with lack of FasL induction was observed in the resistant sublines [115,130]. Similarly, using testicular tumor cells with different sensitivities towards cisplatin it was shown that cisplatin sensitivity is dependent on the activation of the FasR/FasL system (CD95 pathway), and that loss of cisplatin-induced activation of the FasR/FasL system resulted in cisplatin resistance [120].

To date only limited information is available regarding the regulation of members of the SAPK/JNK-p38-FasL pathway in tumor samples. It has been reported that testicular germ cell tumors show a high expression of FasL, which is in line with *in vitro* observations [131]. However, no data are reported about the activation of the JNK signalling cascade in cisplatin-resistant tumors.

4.3. Anti-apoptotic proteins and cisplatin resistance

In both preclinical systems and clinical samples a number of anti-apoptotic proteins have been associated with cisplatin resistance (Fig. 2). Expression of Bcl-2 and Bcl-x_L resulted in cisplatin resistance in various cancer cell lines (for example [132,133]). In patients with

ovarian carcinoma, expression of Bcl-x_L was associated with a decreased response to platinum chemotherapy [134], while no association between response and Bcl-2 expression was observed in breast cancer patients [135].

The inhibitor of apoptosis (IAP) gene family encodes proteins which have been shown to be endogenous inhibitors of caspases, thus resulting in inhibition of cell death. Among several IAP proteins identified, the X-linked inhibitor of apoptosis (XIAP) appears to be the most potent regulator of apoptosis. In preclinical studies XIAP has been implicated in cisplatin resistance. Acquisition of cisplatin resistance was associated with enhanced expression of XIAP in ovarian carcinoma cell lines [136]. Targeting XIAP with RNA interference enhanced cisplatin chemosensitivity in ovarian cancer cells [137] and esophageal cancer cells [138]. Similarly chemosensitivity in prostate cancer cells was potentiated by combined treatment of cisplatin with XIAP antisense oligonucleotides, and it was concluded that abrogation of XIAP expression is essential for therapeutic apoptosis and enhanced chemotherapy sensitization [139].

The clinical relevance of XIAP for the response to cisplatin chemotherapy is unclear. In ovarian cancer tissue no association between XIAP expression and response to chemotherapy was found [135]. An inverse correlation between XIAP expression and pathological response was observed in tissues of advanced bladder cancer patients, however, this was not significant [140]. In the same study, it could be demonstrated that a high level of the XIAP-associated factor 1 protein (XAF1) in bladder cancer tissue resulted in a better prognosis after cisplatin-based chemotherapy [140]. XAF1 antagonizes the anti-apoptotic action of XIAP by directly inhibiting the anti-caspase activity of XIAP [141], which most likely resulted in increased sensitivity towards cisplatin.

Survivin, another member of the IAP family, exerts its anti-apoptotic function also by inhibition of caspase activation (Fig. 2). It has been shown that cisplatin activates the PI3K/AKT/survivin pathway, which in part protects cells from cisplatin-induced apoptosis [142]. An association of survivin levels with cisplatin resistance has been reported in various cancer-derived cell lines. Cisplatin-resistant thyroid cancer cells showed increased expression of survivin, and silencing of survivin by RNA interference restored sensitivity to cisplatin. It was concluded that increased expression of survivin contributes to the acquisition of permanent resistance to cisplatin [143]. Similarly, siRNA against survivin sensitized lung cancer cells to cisplatin [142]. In HNSCC cell lines and malignant pleural mesotheliomas antisense oligonucleotides against survivin resulted in an enhancement of cisplatin toxicity [107,144]. The investigation of survivin expression in cancer tissues revealed an inverse correlation to the overall survival of patients following cisplatin therapy. In gastric carcinoma, expression of survivin was significantly upregulated in cancer tissue compared to normal tissue and it was negatively associated with overall survival of patients undergoing cisplatin-based chemotherapy [145]. Similarly, a negative correlation between survivin gene expression and response to cisplatin chemotherapy was observed in patients with NSCLC [146] and esophageal cancer [147].

Taken together, the clinical relevance of factors involved in cisplatin-induced apoptotic cell death pathways is still emerging. More information about a relationship between the activation of apoptotic cell death pathways and clinical outcomes are needed as this may identify novel targets for pharmacological intervention.

5. Strategies for overcoming cisplatin resistance

Based on the described mechanisms of cisplatin resistance, several strategies have been proposed to circumvent the resistance phenotype. They include combination of cisplatin with modulators of players involved in cisplatin resistance, combination of cisplatin with
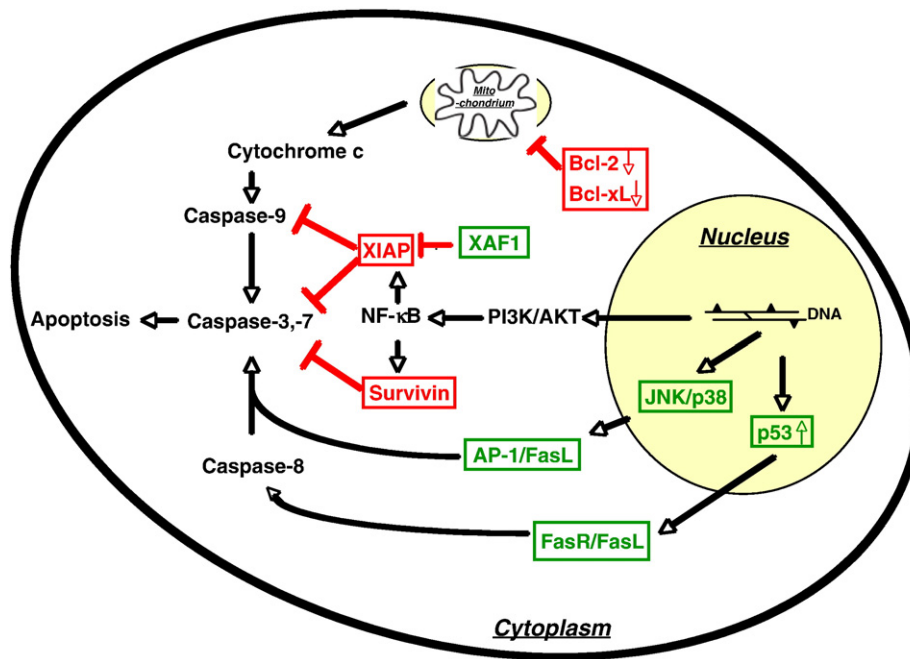
Fig. 2. Cellular responses to cisplatin. Cisplatin lesions induce members of pro-apoptotic pathways (green) leading to caspase activation. Anti-apoptotic factors (red) counteract caspase activation therefore inhibiting cisplatin-induced apoptosis.

drugs targeting specifically cancer cells, and finally the development of new platinating drugs.

5.1. Cisplatin and modulators of cisplatin resistance

Specifically targeting the resistance mechanism can be achieved by increasing cisplatin accumulation in tumors, interfering with cisplatin detoxification pathways, and modulating DNA repair (Table 2). In a preclinical study it has been shown that the proteasomal inhibitor bortezomib prevents the degradation of the influx transporter hCTR1 in ovarian cancer cells, which was accompanied by an increase in cisplatin accumulation in tumor cells and antitumor efficacy [148]. Clinical studies have now to clarify whether combined treatment with cisplatin and bortezomib will result in a survival advantage in patients with ovarian cancer.

Modulation of the glutathione system by glutathione depletion or GST blocking agents significantly enhanced cisplatin toxicity in bladder cancer cell lines [149]. Similarly, the anticancer agent 6-(7-nitro-2,1,3-benzoxadiazol-4-ylthio)hexanol (NBDHEX), an inhibitor of GST, showed a strong effect reducing cisplatin resistance in human osteosarcoma cell lines [150]. It is therefore suggested that NBDHEX applied together with cisplatin could be a new therapeutic possibility for patients with osteosarcoma who failed to respond to cisplatin chemotherapy. A different approach is to make use of the increased levels of GST, which have been observed in some cisplatin-resistant tumors. TLK286 (canfosfamide), a prodrug that is activated by GST to produce a nitrogen mustard alkylating agent [151] has shown clinical activity in platinum-resistant ovarian cancer patients [152].

In general, the inhibition of DNA repair has the potential to enhance the cytotoxicity of anticancer agents as preclinical studies have confirmed that modulation of repair pathways can enhance the sensitivity to DNA damaging agents. For a number of DNA repair inhibitors clinical studies are now under way (for review see [153,154]). For example, O^6-methylguanine-DNA methyltransferase (MGMT), base excision repair (BER) and PARP are involved in the repair of lesions induced by alkylating agents, and promising clinical activity of inhibitors of these DNA repair proteins has been reported [155,156].

Due to the observation that clinical resistance to platinum therapy is often correlated with increased levels of ERCC1, one can envisage ERCC1 as a key target to modulate cisplatin resistance. As ERCC1 has no known catalytic activity, ERCC1–XPF or ERCC1–XPA protein–protein interactions could be targets for sensitization strategies. The Chk1 inhibitor UCN-01, which reduces the ERCC1–XPA interaction, has been shown to increase cisplatin toxicity [157]. However, enzymatic activities have proven to be more successful targets in the pharmaceutical industry than disruption of protein–protein interactions. Therefore, targeting the endonuclease activity of XPF might also be a successful approach. Furthermore, based on the observation of a correlation between ERCC1 expression and cisplatin resistance clinical trials are now under way to customize chemotherapy based on ERCC1 expression in patient tumor tissue [158]. It is hoped that individualized chemotherapy may improve response and/or reduce toxicity on normal tissue of cisplatin in cancer patients.

As hypermethylation of MLH1 CpG islands in ovarian cancers was correlated with resistance towards cisplatin and poor survival [110],

Table 2
Modulators of cisplatin resistance mechanisms.

Resistance mechanism	Modulator	Action of modulator	Preclinical/clinical data
Copper transporter 1 (Ctr1)	Bortezomib	Prevents degradation of Ctr1	Increased cisplatin accumulation
glutathione-S-transferase (GST)	NBDHEX	Inhibitor of GST	Reduced cisplatin resistance
glutathione-S-transferase (GST)	TLK286	Activation by GST	Phase II study
ERCC1 (nucleotide excision repair)	UCN-01	Reduction of ERCC1–XPF interaction	Increased cisplatin toxicity
MLH1 (mismatch repair)	Decitabine	Demethylation of silenced genes	Phase I study

gene methylation could be a target for resistance reversal in ovarian cancer. The DNA demethylating agent decitabine might result in re-expression of silenced genes and therefore reverse the resistance phenotype. In a phase I study it could be confirmed that decitabine could be combined safely with platinating agents [159].

5.2. Combination of cisplatin with drugs targeting cancer cells

Combination of cisplatin with other drugs has been proven to be a successful therapeutic approach. Special emphasis has recently been given to the co-administration of cisplatin and other platins with drugs specifically targeting cancer cells. For example, the combination of cisplatin and trastuzumab, an antibody raised against the EGF receptor subtype HER2, has shown promising clinical activity in patients with advanced breast cancer that overexpress HER2 [160,161]. The addition of bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), to platinum-based chemotherapy resulted in an improved response and survival in patients with non-small cell lung cancer showing that bevacizumab in combination with platinum-based chemotherapy offers a clinical benefit for patients with non-small cell lung cancer [162,163].

5.3. Development of new platinum drugs

The introduction of new partially or completely non-cross-resistant cisplatin analogous is a different approach to circumvent cisplatin resistance (for review see [164,165]). Carboplatin and oxaliplatin, although not new drugs, show some circumvention of acquired cisplatin resistance in cancer cell lines [166]. For oxaliplatin, the lack of cross-resistance seems to be due to differences in uptake mechanisms. Thus, in contrast to cisplatin, cellular accumulation of oxaliplatin seems to be less dependent on Ctr1. In addition, MMR proteins do not recognize oxaliplatin-induced DNA lesions. Both carboplatin and oxaliplatin are approved for clinical use, with oxaliplatin being effective in colon cancers, which were previously thought to be resistant to platinum compounds [167].

In preclinical studies it has been shown that the new generation cisplatin analogues satraplatin and picoplatin are able to overcome acquired cisplatin resistance in osteosarcoma and ovarian cancer cell lines [168,169]. Satraplatin and picoplatin, now in clinical trial, introduce bulkier DNA lesions than cisplatin, which might be more difficult for the cells to remove or tolerate by replication bypass, i.e. translesion synthesis (TLS) [83,84]. In addition, picoplatin appears to be less reactive towards thiol-containing molecules than cisplatin therefore escaping detoxification by GSH and MT [170,171]. Satraplatin and picoplatin have shown promising clinical activity in prostate cancer and non-small cell lung cancer [165]. In a recent phase II study picoplatin showed clinical efficacy in small cell lung cancer patients who were refractory to other platinum compounds [172].

6. Concluding remarks

Cisplatin plays a major role in the treatment of a variety of malignancies including testicular, head and neck, lung, ovarian and bladder cancer. Unfortunately, the therapeutic effect of cisplatin is often limited due to intrinsic or acquired tumor cell resistance. Potential determinants of cisplatin resistance such as transport, detoxification, DNA repair, DDR and apoptosis signalling proteins have been identified in preclinical models. However, the clinical significance of all these mechanisms is not fully explored and only evolving. Therefore, a better understanding about the resistance mechanisms in tumors is essential for developing therapeutic strategies aimed at circumventing cisplatin resistance for improving cancer therapy.

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