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Review Article

Cellular Responses to Cisplatin-Induced DNA Damage

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Cisplatin is one of the most effective anticancer agents widely used in the treatment of solid tumors. It is generally considered as a cytotoxic drug which kills cancer cells by damaging DNA and inhibiting DNA synthesis. How cells respond to cisplatin-induced DNA damage plays a critical role in deciding cisplatin sensitivity. Cisplatin-induced DNA damage activates various signaling pathways to prevent or promote cell death. This paper summarizes our current understandings regarding the mechanisms by which cisplatin induces cell death and the bases of cisplatin resistance. We have discussed various steps, including the entry of cisplatin inside cells, DNA repair, drug detoxification, DNA damage response, and regulation of cisplatin-induced apoptosis by protein kinases. An understanding of how various signaling pathways regulate cisplatin-induced cell death should aid in the development of more effective therapeutic strategies for the treatment of cancer.

1. Introduction

Cisplatin was discovered fortuitously by Dr. Rosenberg in 1965 while he was examining the effect of electromagnetic field on bacterial cell growth [1, 2]. Since the active principle that inhibited bacterial cell division was identified to be cisplatin, he anticipated that it would also inhibit the proliferation of rapidly dividing cancer cells. Cisplatin was indeed demonstrated to possess antitumor activity in a mouse model [3] and was first used in the clinical trial almost 30 years ago. Since its approval by the Food and Drug administration in 1978, cisplatin continues to be one of the most effective anticancer drugs used in the treatment of solid tumors.

Cisplatin has been used as a first-line therapy for several cancers, including testicular, ovarian, cervical, head, and neck and small-cell lung cancers either alone or in combination with other anticancer agents. It is also used as an adjuvant therapy following surgery or radiation. In addition to cisplatin, its analogs, such as carboplatin and oxaliplatin, are also currently being used in the clinic. However, patients who initially respond to cisplatin therapy often develop resistance to the drug during the course of the treatment.

The success of cisplatin therapy is compromised due to dose-limiting toxicity, especially nephrotoxicity as well as resistance by tumor cells to cisplatin. Cellular resistance to cisplatin could be either intrinsic or acquired. The clinically acquired resistance can be caused by decreased drug accumulation which includes reduced uptake or increased efflux of cisplatin, increased drug detoxification by cellular thiols, increased DNA repair or tolerance of cisplatin-damaged DNA and the ability of the cancer cells to evade cisplatin-induced cell death. Numerous studies have focused on the drug-target interactions, cellular pharmacology, and pharmacokinetics of cisplatin. Another active area of research has been to develop analogs of cisplatin to minimize toxicity and circumvent cisplatin resistance.

The antitumor activity of cisplatin is believed to be due to its interaction with chromosomal DNA [4]. Only a small fraction of cisplatin, however, actually interacts with DNA and the inhibition of DNA replication cannot solely account for its biological activity [5]. In addition, the efficacy of chemotherapeutic drugs depends not only on their ability to induce DNA damage but also on the cell's ability to detect and respond to DNA damage [6]. Following DNA damage, cells may either repair the damage and start

progressing through the cell cycle or if they cannot repair the damage, cells proceed to die [5]. Cisplatin, like many other chemotherapeutic drugs, can induce apoptosis. Thus, the signaling pathways that regulate apoptosis have significant impact on deciding cellular responsiveness to cisplatin. There are many excellent reviews on cisplatin and its analogues [7–15]. In this paper, we primarily focused on recent studies on cellular responses to cisplatin-induced DNA damage although we briefly discussed steps leading to cisplatin-induced DNA damage. This comprehensive paper should not only benefit researchers in the field of cisplatin but also benefit those interested in mechanisms of chemoresistance and targeted therapy.

2. Biotransformation of Cisplatin

Cisplatin or *cis*-diamminedichloroplatinum(II) is a neutral, square-planar, coordination complex of divalent Pt [8]. The *cis* configuration is required for its antitumor activity [16]. It has two labile chloride groups and two relatively inert amine ligands. Cisplatin undergoes hydrolysis in water. The chloride concentration is an important factor in determining the hydrolysis or aquation of cisplatin. The high chloride concentration (~103 mM) of blood plasma prevents the hydrolysis of cisplatin. Upon entering the cell, the chloride concentration drops down to 4 mM which facilitates the aquation process [17]. The aquated form of cisplatin is a potent electrophile and reacts with a variety of nucleophiles, including nucleic acids and sulfhydryl groups of proteins.

3. Accumulation of Cisplatin Inside Cells

Cisplatin and its analogues were initially thought to enter cells by passive diffusion because cisplatin uptake was linear, nonsaturable and could not be competed with platinum analogs [4–6, 17]. Although decreased accumulation of cisplatin is often associated with acquired resistance to cisplatin, few or no changes were observed in the plasma membrane function in the cisplatin-resistant cell lines as compared to the parental cells [18–20]. In 1981, it was first proposed that cisplatin could be transported actively via the carrier-mediated transport [21]. Several transporters, including the Na^+, K^+-ATPase [22] and members of solute carrier (SLC) transporters [11] have been implicated in facilitating the entry of cisplatin into the cells. The plasma membrane copper transporter-1 (CTR1), a member of the SLC family, gained particular attention since a defect in *Ctr1* gene decreased cisplatin accumulation in yeast [23, 24]. In addition, cisplatin and carboplatin accumulation was attenuated in mouse embryonic fibroblasts from *ctr1*$^{-/-}$ animals compared to wild-type animals [18]. Interestingly, both copper and cisplatin were shown to cause rapid downregulation of CTR1 in ovarian cancer cells by the proteasome-mediated pathway [19]. While CTR1 appears to transport cisplatin and its analogs, there is little decrease in CTR1 when cells acquire resistance to cisplatin. A recent study demonstrated that copper transporter-2 or CTR2 limits accumulation of cisplatin and the level of CTR2 correlates with the sensitivity of ovarian carcinoma cells to cisplatin [25]. The organic cationic transporters SLC22 family of proteins have also been shown to participate in cisplatin influx [11]. Thus, cisplatin can enter cells by passive or facilitated diffusion and by active transport. Depending on the cellular context, multiple transporters may be involved in cisplatin uptake. Therefore, it is difficult to correlate cisplatin sensitivity/resistance with a particular transporter.

Many cell lines with acquired resistance to cisplatin often exhibit reduced drug accumulation. Unlike multidrug resistance (MDR), drug efflux does not appear to be the major cause of cisplatin resistance. Kawai et al. first reported that a 200-kDa plasma membrane glycoprotein is overexpressed in murine thymic lymphoma cells selected for resistance to cisplatin, which correlated with reduced accumulation of cisplatin in the cells [26]. The increased expression of this protein correlated with the degree of cisplatin resistance [26]. There was, however, no follow-up study to establish the importance of this protein in conferring cisplatin resistance. The ATP-dependent glutathione-conjugated efflux pump and copper transporters ATP7A and ATP7B have been implicated in cisplatin export [20]. It is generally believed that reduced cisplatin accumulation in cisplatin resistant cells is due to decrease in uptake of cisplatin rather than an increase in drug efflux [7, 27].

4. Formation and Repair of Cisplatin DNA Adduct

DNA is thought to be the primary biological target of cisplatin [17, 28, 29]. The platinum atom of cisplatin forms covalent bonds with the N^7 position of purine bases to form 1,2- or 1,3-intrastrand crosslinks and a lower percentage of interstrand crosslinks. Cisplatin resembles bifunctional alkylating agents. The intrastrand crosslink between two adjacent G residues is believed to be the critical lesion responsible for cisplatin cytotoxicity. Formation of cisplatin-DNA adducts interferes with DNA replication and transcription. The interstrand and intrastrand crosslinks disrupt the structure of the DNA. This alteration in the structure is recognized by the cellular proteins to repair cisplatin-induced DNA damage. Increased repair of cisplatin-induced DNA damage has been associated with cisplatin resistance.

4.1. Cisplatin and Nucleotide Excision Repair Pathway. Since the intrastrand cross-link is the major lesion caused by cisplatin-induced DNA damage, it is primarily repaired via the nucleotide excision repair (NER) system. Xeroderma Pigmentosum (XP) is a disorder caused by deficiency of genes involved in NER. Cells derived from XP patients are exquisitely sensitive to cisplatin [30]. In addition, the favorable response of testicular cancer to cisplatin was associated with low levels of XP complementation group A (XPA) and excision repair cross-complementation group I (ERCCI), which participate in NER [31, 32]. A number of studies correlated the overexpression of ERCC1 or XPA proteins with cisplatin resistance [31–34]. The existence of ERCC1 exon VIII alternative splicing was observed in ovarian

cancer cells [35]. Although this splicing did not affect the level of ERCC1, it decreased its excision repair function. In addition, epigenetic changes, such as hypermethylation of ERCC1, which inversely correlated with ERCC1 mRNA levels, have been suggested as a mechanism for enhanced cisplatin sensitivity [36]. A recent study demonstrated that XPA binding domain of ERCC1 was required for the repair of cisplatin-damaged DNA [37]. A double knockdown of XPF/ERCC1 complex was shown to be very effective in enhancing cisplatin sensitivity in non-small cell lung cancer cells [38]. An antisense DNA against XPA sensitized lung adenocarcinoma cells to cisplatin [34]. Recently, it has been reported that treatment of rat spiral ganglion neurons with cisplatin induced the mRNA levels of XPA and XPC along with nuclear translocation of these enzymes, thus decreasing the rate limiting step in the NER pathway [39]. This can provide a plausible mechanism by which cisplatin induces NER. Kang et al. made an interesting observation that XPA was regulated in a circadian fashion in the mouse liver, but not in the testis [40]. Removal of cisplatin-DNA adducts also followed a circadian pattern in the extracts derived from the liver. The authors proposed that chronochemotherapy could be more effective in the treatment of cancers in which XPA removes cisplatin-DNA adducts in a circadian fashion. Thus, the cisplatin-induced DNA repair employing the NER process is multilayered including epigenetic, transcriptional, and posttranslational regulation.

NER is also linked to the cellular signaling pathways. It has been reported that the NER process may prevent cisplatin-induced apoptosis by activating the ataxia telangiectasia mutated (ATM) pathway which is recruited to the damaged DNA through XPC [41]. Lack of functional p53 has been associated with persistence of cisplatin-induced intrastrand cross-links, suggesting the importance of p53 in regulating NER of cisplatin-damaged DNA [42]. Functional NER was also required for cisplatin-induced transcription of Bcl-xL via nuclear factor-kappa B (NF-κB) [43].

In addition to NER, cisplatin can also induce transcription-coupled repair (TCR). The intrastrand crosslink stalls RNA polymerase II to trigger TCR [44]. It has been reported that p53 protects against cisplatin-induced apoptosis in a TCR-dependent manner [30]. In addition, the homology-directed DNA repair (HR) that allows error-free repair of the double-strand breaks caused by the excision of cisplatin-DNA adducts has been implicated in the repair of cisplatin-induced DNA damage [45]. It has been reported that mouse mammary tumors containing irreparable null alleles of *Brca1* gene, which is involved in DNA double strand break repair, do not become resistant to cisplatin. Bypass of cisplatin-DNA adduct has also been associated with cisplatin resistance. DNA polymerase-eta could replicate across intrastrand cross-link between cisplatin and two adjacent G residues [46].

4.2. Cisplatin and Mismatch Repair Pathway. Mismatch repair (MMR) system recognizes cisplatin-induced DNA damage, but instead of increasing cell viability, MMR system was shown to be important for cisplatin-mediated cytotoxicity [47]. DNA mismatch repair protein, MutSα recognized DNA lesions formed by cisplatin [48–50], and mutations in MSH1 or MLH1 genes of the MMR system were observed in cisplatin-resistant cells [51–53]. Recently, the proapoptotic function of cisplatin was shown to be mediated in an MSH2/MSH6-dependent manner [54]. MLH1-proficient cells were more sensitive to cisplatin compared to MLH1-deficient cells. Cell death by cisplatin was associated with significant proteolysis of MLH1, caused by destabilization of X-linked inhibitor of apoptosis protein (XIAP), resulting in caspase activation [55]. The repair function of MMR proteins has been reported to be uncoupled from their function in mediating cisplatin-induced cell death [56–58]. Since the primary mechanism of cisplatin involves DNA damage and p53 is also involved in DNA damage signaling, there are many studies that correlate cisplatin and DNA damage and repair with p53 activity [59–62]. It has been reported that cisplatin enhances the interaction between mismatch repair protein MLH1/postmeiotic segregation increased 2 (PMS2) and p73 triggering apoptosis in mismatch repair-proficient cells [60].

5. Interaction of Cisplatin with Cellular Thiols

Although the major target of cisplatin is the nuclear DNA, it exhibits a high affinity towards sulfur donors such as cysteines and methionines forming stable Pt-S bonds. This competes with the affinity towards the nitrogen atom in the DNA thus contributing towards resistance against the cytotoxic action of cisplatin [63]. The abundant intracellular thiols involved in the drug resistance are glutathione and metallothionein.

5.1. Interaction of Cisplatin with Glutathione. When cancer cells are exposed to cisplatin, the platinum atom in cisplatin is chelated by glutathione (GSH) and the glutathione-Pt complex is effluxed from the cell in an ATP-dependent manner by the glutathione transporter family, termed the GS-X pumps [64]. It was initially noted that cells that are resistant to cisplatin have elevated levels of glutathione [65]. However, recent studies with cisplatin-resistant cancer cell lines seem to suggest otherwise [66, 67]. Based on NMR studies, Kasherman et al. reported that the higher levels of GSH do not correlate with decreased sensitivity to cisplatin [68]. In agreement with this study, Chen et al. suggested that increased levels of GSH might sensitize cells to cisplatin by upregulation of the copper transporter hCtr1 [69]. Therefore, whether overexpression of glutathione contributes to or combats cisplatin resistance is still under debate.

Apart from GSH, the glutathione S-transferase P1-1 (GSTP1-1) enzyme has also been associated with resistance to cisplatin-based chemotherapy [70, 71]. Pasello et al. demonstrated that increased levels of GSTP1 were associated with cisplatin resistance in osteosarcoma cell lines and a higher relapse rate and poor prognosis in high-grade osteosarcoma patients [72]. In contrast, a recent study by Peklak-Scott et al. suggested that a high level of cisplatin resistance may not be due to conjugation of

cisplatin to glutathione by GSTP1 [73]. Other enzymes in the glutathione transferase family, such as the GSTμ or the GSTO1-1, have also been implicated in contributing towards cisplatin resistance [74, 75]. Thus, although a great deal of work has been focused on the correlation of glutathione and its conjugating enzymes towards cisplatin resistance, further studies are needed to explore this in detail.

5.2. Interaction of Cisplatin with Metallothionein. Metallothioneins (MT) are cysteine-rich proteins, which consist of 61-68 amino acids of which 20 are cysteins. The four isoforms of MTs (MT1-MT4) are ubiquitously expressed in humans and are inducible by a variety of drugs, including cisplatin [76]. They are involved in zinc and copper homeostasis, heavy metal detoxification, and protection from apoptosis. Initial reports observed an increased expression of metallothionein correlating with cisplatin resistance in ovarian carcinoma cell lines [77]. We have also seen that a wide variety of human cancer cell lines with acquired resistance to cisplatin overexpressed metallothionein and ectopic expression of metallothionein conferred cisplatin resistance [78]. Recent reports also suggest that the increased expression of metallothionein correlates with cellular resistance against cisplatin [79–81].

The ubiquitously occurring metallothionein isoforms, MT-1 and MT-2, have been shown to react faster with cisplatin [82], compared to glutathione [83, 84]. The basal levels of MT-1 and MT-2 are often significantly increased in cancer cells [78, 85], resulting in even stronger scavenging of divalent platinum, and contributing to acquired resistance against cisplatin [78, 86, 87]. MT-3 isoform was initially thought to be unresponsive to the platinum drugs [81]. Recent reports, however, suggest that MT-3 is overexpressed in hypoxic conditions, and the reaction between MT-3 and Pt(II) is kinetically preferred [81]. The authors further proposed that the Zn(II) released from this reaction can result in the upregulation of the MT-1 and MT-2 isoforms. Thus, metallothionein isoforms play an important role in contributing towards cisplatin resistance.

6. Cisplatin and DNA Damage Signaling

Various stress signals generate DNA lesions that may lead to mutations and genomic instability. Following DNA damage, cell cycle checkpoints are activated to delay cell-cycle progression to provide time for DNA repair or eliminate genetically unstable cells by inducing cell death. It is now recognized that inhibition of DNA replication is not sufficient to explain cisplatin cytotoxicity. How cells respond to cisplatin-induced DNA damage plays a major role in the ultimate decision whether a cell should live or die following cisplatin treatment.

6.1. p53 and Cisplatin-Induced DNA Damage Response. The tumor suppressor protein p53 is considered as the "guardian of genome". It plays a critical role in eliciting cellular responses to DNA damage. p53 is a short-lived protein which is primarily degraded via the ubiquitin proteasome-mediated pathway [30, 88]. The E3 ubiquitin ligase Mdm2 is a transcriptional target of p53 and regulates p53 expression via a negative feedback loop [30]. DNA damage results in the activation of ATM and/or ATM- and Rad3-related (ATR), resulting in phosphorylation and stabilization of p53 [88]. p53 can transactivate genes involved in cell cycle progression (e.g., p21), DNA repair (e.g., growth arrest and DNA damage-inducible 45, GADD45), and apoptosis (e.g., Bax) [89].

Fujiwara et al. first demonstrated that adenoviral-mediated delivery of p53 into small-cell lung cancer cells induced massive apoptosis both in monolayer cultures and in tumor xenografts upon treatment with cisplatin [90]. Introduction of wild-type p53 by adenovirus vector also sensitized ovarian cancer cells to cisplatin [91–93]. Several proteins, including cyclin-dependent kinase inhibitor p21, ATR, and checkpoint kinase (CHK2) have been implicated in p53-mediated apoptosis [94–97]. In addition, tumor cells lacking functional p53 were more resistant to cisplatin than cells that contained functional p53 and the resistant cell lines were sensitized to cisplatin upon reconstitution with wild-type p53 [98, 99]. p53 itself has been shown to bind cisplatin-modified DNA [100]. In addition, cisplatin was shown to induce nitrosylation of p53 preventing its mitochondrial translocation [101].

p53 can regulate cisplatin-induced cell death by several mechanisms. Degradation of FLIP (FLICE-like inhibitory protein) has been reported to be necessary for p53-induced apoptosis in response to cisplatin [102, 103]. p53 also promotes cisplatin-induced apoptosis by directly binding and counteracting the antiapoptotic function of Bcl-xL [104]. Although the phosphatase and tensin homolog (PTEN) is believed to inhibit phosphoinositide 3-kinase (PI3K)/Akt, overexpression of PTEN was shown to involve p53-mediated apoptotic cascade in cisplatin-resistant ovarian cancer cells independent of PI3K/Akt pathway [105]. The nutrient-sensor AMP-kinase (AMPK) was shown to be activated by cisplatin in AGS and HCT-116 cancer cells and inhibition of AMPK enhanced cisplatin-induced apoptosis by causing hyperinduction of p53 [106].

One of the major side effects of cisplatin therapy is nephrotoxicity and the involvement of p53 in cisplatin-induced nephrotoxicity has been investigated. p53 induced proapoptotic Bcl-2 family member PUMAα in renal tubular cells upon treatment with cisplatin, and dominant-negative p53 suppressed the expression of PUMAα. This study was extended in C57 mice. Acute renal failure upon cisplatin treatment was abrogated in p53-deficient C57 mice and this was associated with little or no induction of PUMAα [107]. CHK2 has also been implicated in apoptosis of renal cells and tissues as a result of cisplatin-induced p53 activation [94]. A study by Yang et al. revealed that caspase-6 and -7 are transcriptional targets of p53 [108]. Thus, induction of p53 by cisplatin resulted in the activation of these caspases contributing to nephrotoxicity [108]. Inhibition of p53 by pharmacological inhibitor or knockout of p53 in mice suppressed caspase-6 and -7 transactivation and protected against nephrotoxicity. Recently, microRNAs have also been

shown to play a major role in cisplatin nephrotoxicity. miR-34a is induced by cisplatin via p53 and plays a cytoprotective role in the survival of proximal tubular cells [109].

Although a plethora of literature exists on the role of p53 in contributing towards cisplatin cytotoxicity, p53 has also been associated with cisplatin resistance. MCF-7 breast cancer cells containing wild-type p53 are highly resistant to cisplatin but disruption of p53 by the introduction of human papilloma virus (HPV) in MCF-7 cells sensitized these cells to cisplatin [110]. Ovarian cancer cells selected for cisplatin resistance exhibited higher levels of p53 compared to cisplatin-sensitive counterpart [111]. Although p53 level is low in HeLa cells due to degradation of p53 by HPV, it was elevated in cisplatin-resistant HeLa cells [112]. Studies have also shown that mutations in p53 contributed to cisplatin resistance in different cancer models [113–116].

Although p53 plays an important role in cisplatin-induced DNA damage response, p53-negative cells also respond to cisplatin-induced DNA damage, suggesting alternate pathways of sensing cisplatin-induced DNA damage.

6.2. c-Abl and Cisplatin-Induced DNA Damage Response. The tyrosine kinase c-Abl plays an important role in stress response to DNA damaging agents. It belongs to the non-receptor tyrosine kinases and contains nuclear localization motifs and nuclear export signals. Thus, it can shuttle between the nucleus and cytoplasm. Nuclear import of c-Abl was shown to be necessary for DNA damage-induced apoptosis [117]. It is activated in response to cisplatin causing activation of c-Jun-N-terminal kinase (JNK)/stress-activated protein kinase (SAPK) [118]. c-Abl-deficient cells fail to activate JNK. Nuclear c-Abl can associate with and phosphorylate MEK kinase 1 (MEKK1) in response to DNA damage resulting in the activation of JNK/SAPK [119]. Nehmé et al. [120] demonstrated that activation of c-Abl and JNK is contingent upon the recognition of cisplatin-induced DNA damage by the MMR system since c-Abl response is absent in MMR-deficient cells. They further demonstrated that the activation by these pathways is specific to cisplatin and not to the cisplatin analogue oxaliplatin, thus highlighting the importance of the MMR system to specifically recognize cisplatin-DNA adducts [120, 121].

Interestingly, MMR/c-Abl cooperates with p73, a member of the p53 family, to trigger apoptosis [122]. Cisplatin caused induction of p73 in several cancer cell lines and in mouse embryonic fibroblasts (MEF), which were proficient in mismatch DNA-repair pathway but not in MEF deficient in c-Abl or MMR [122]. Activation of c-Abl in response to cisplatin led to phosphorylation and stabilization of p73 [123, 124]. Phosphorylation of p73 can also increase its proapoptotic function by dissociating itself from p63, another member of the p53 family. p63 can bind to and counteract the proapoptotic function of p73 [125]. In addition, c-Jun was shown to enhance p73 stability and transactivation activity by preventing its degradation via the proteasomal pathway [126]. Binding of the transcription coactivator Yap1 also prevents proteasomal degradation of p73 and results in the recruitment of p300 to trigger transcription of proapoptotic genes. c-Abl can directly phosphorylate Yap1, increasing its stability and affinity for p73 [127]. Phosphorylation of Yap1 can dictate whether p73 will transactivate proapoptotic or growth arrest genes [127]. A recent study suggests that c-Abl can regulate the function of p63. Phosphorylation of p63 at Tyr residue by c-Abl stabilizes it causing an increase in its proapoptotic function [128].

Cisplatin can trigger cleavage of c-Abl which is a substrate for caspase and proteolytic cleavage of c-Abl was shown to be important for cisplatin-induced apoptosis [129]. Activation of p38 MAPK is critical for regulating cisplatin activity. Galan-Moya et al. [130] recently reported that c-Abl activates p38 MAPK independent of its tyrosine-kinase activity but by stabilizing MKK6, the upstream kinase of p38 MAPK. This study provides an explanation why the c-Abl inhibitor imatinib fails to inhibit p38 MAPK [130]. Thus, c-Abl is an important mediator of cisplatin-induced DNA damage response and acts in cooperation with the siblings of p53 and MAPK pathways to trigger cisplatin-induced apoptosis.

7. Regulation of Cisplatin-Induced Cell Death by Protein Kinases

Cisplatin primarily induces cell death by apoptosis and a defect in apoptotic signaling could also confer cisplatin resistance. There are two major pathways of cell death [131, 132]. The extrinsic pathway is initiated when ligands bind to the tumor necrosis factor-α (TNFα) receptor superfamily followed by oligomerization and recruitment of procaspase-8 via adaptor molecules to form the death-inducing signaling complex (DISC). The intrinsic pathway is initiated by cellular stress, such as DNA damage, resulting in release of cytochrome-c from the mitochondria causing activation of procaspase-9 through the interaction with apoptosis promoting activating factor-1 (APAF-1) and formation of an active apoptosome complex. Bcl-2 family proteins regulate DNA damage-induced apoptosis by regulating the release of mitochondrial cytochrome c in response to DNA damage. Cisplatin-induced genotoxic stress activates multiple signal transduction pathways, which can contribute to apoptosis or chemoresistance.

7.1. Cisplatin and Protein Kinase C. Protein kinase C (PKC) is a family of closely related phospholipid-dependent enzymes that play critical roles in signal transduction and cell regulation [133–136]. Based on the structure and biochemical properties they are grouped as conventional (α, βI, βII, and γ), novel ($\delta, \varepsilon, \eta$, and θ) and atypical (ζ and ι) PKCs. Tumor-promoting phorbol esters are potent activators of PKCs but persistent treatment with phorbol esters can induce downregulation or degradation of phorbol ester-sensitive conventional and novel PKCs.

We inadvertently found that the PKC signal transduction pathway can regulate cisplatin sensitivity. In the meantime, Hofmann et al. reported that inhibition of PKC by quercetin or downregulation of PKC by the phorbol ester, 12-*O*-tetradecanoylphorbol-13-acetate (TPA) could enhance the antiproliferative activity of cisplatin [137]. In contrast,

Isonishi et al. [138] and we [139] simultaneously reported that activation of PKC by phorbol esters could enhance sensitivity of human ovarian cancer 2008 and human cervical cancer HeLa cells to cisplatin. There were contrasting reports whether activation or downregulation of PKC was necessary for cisplatin sensitization [138, 140]. Although TPA is a useful tool as a pharmacological agent to study PKC function, it is a tumor promoter and therefore cannot be used in the clinic. We first showed that bryostatin 1, a partial PKC agonist which lacks tumor promoting activity, also sensitized HeLa cells to cisplatin [141]. Based on the preclinical studies, Phase II trial using combination of bryostatin 1 and cisplatin was initiated in advanced recurrent cervical carcinoma but was not very effective [142]. Combination of bryostatin 1 and cisplatin had minimal toxicity in patients with refractory nonhematological malignancies although only four patients achieved an objective response [143]. This may be because bryostatin 1 is a partial agonist and its regulation is complex. One of the caveats with these earlier studies to define the role of PKC in regulating cisplatin sensitivity was that PKC activation and downregulation was monitored based on PKC activity assay which does not discriminate among PKC isozymes. We now know that PKC isozymes may have distinct and even opposite effects on cisplatin-induced cell death [144]. Another shortcoming with these studies was the use of pharmacological agents that lack absolute specificity to PKC.

An increase in novel PKCδ or -ε and a decrease in conventional PKCs have been associated with acquired resistance to cisplatin [145]. However, inhibition of PKCα by Gö 6976 and depletion of PKCα by siRNA enhanced sensitivity of both parental and cisplatin-resistant HeLa cells to cisplatin [146]. Antisense oligonucleotides against PKCα enhanced the antitumor activity of cisplatin against human breast cancer MCF-7, prostate cancer PC3, and human small cell carcinoma H69 cells transplanted in nude mice [147]. Additionally, antisense oligonucleotide against PKCα in combination with cisplatin was effective in patients with non-small cell lung cancer [148]. Furthermore, although PKCα was downregulated in cisplatin-resistant A2780 cells, introduction of PKCα in these cells attenuated cisplatin sensitivity [149]. A recent study demonstrated that inhibition of PKCβ by enzastaurin enhanced cisplatin sensitivity via dephosphorylation of p90 ribosomal S6 kinase and Bad [150]. These results suggest that conventional PKCα and -β function as antiapoptotic proteins. It is not clear why a decrease rather than an increase in cPKCs was associated with cisplatin resistance.

The observation that PKCδ is a substrate for caspase-3 [151] established the importance of this PKC isozyme in apoptotic signaling. It has been reported that treatment of cisplatin-resistant human squamous cell carcinoma SCC-25 (SCC25/CP) cells to cisplatin failed to induce caspase-3 activation and cleavage of PKCδ due to an increase in anti-apoptotic Bcl-xL [152]. Interestingly, the effect of bryostatin 1 on caspase activation and PKCδ downregulation followed similar biphasic concentration response in both parental and cisplatin-resistant HeLa cells [146, 153]. We have shown that PKCδ not only acts downstream of caspase-3 but it can also regulate cisplatin-induced activation of caspase-3 [154]. These studies were based on the effect of rottlerin, a pharmacological inhibitor of PKCδ on cisplatin-induced apoptosis [155]. Although rottlerin caused downregulation of caspase-2 and inhibition of cisplatin-induced apoptosis, the effect of rottlerin on caspase-2 downregulation was not due to inhibition of PKCδ [156]. The effect of PKCδ on cisplatin-induced apoptosis depends on the cellular context. In gastric cancer MKN28 cells, PKCδ was shown to enhance cisplatin-induced caspase activation and cell death via p53 [157]. Overexpression of PKCδ or caspase cleavage-resistant mutant of PKCδ had little effect on cisplatin-induced cell death in human small-cell lung cancer H69 cells which have mutated p53 [158]. On the other hand, knockdown of PKCδ enhanced cisplatin-induced cell death in thyroid cancer by decreasing fos expression [159].

We have shown that overexpression of PKCε contributes to cisplatin resistance by inhibiting cisplatin-induced apoptosis [160]. Integrative genomic approach has identified PKCι as a potential oncogene for ovarian carcinoma [161]. It has also been associated with chemoresistance of glioblastoma multiforme, an aggressive form of brain cancer [162]. The mechanism of PKCι-mediated chemoresistance involved inhibition of p38 MAPK [162]. A recent study suggests that atypical PKCζ can counteract the ability of cisplatin to decrease matrix metalloproteinase-2 secretion [163]. Thus, the effects of PKC on cellular sensitivity/resistance to cisplatin depend on the pattern of the PKC isozymes as well as on the cellular context.

7.2. Cisplatin and MAPK. Mitogen-activated protein kinases (MAPK) are a family of structurally-related serine/threonine protein kinases that coordinate various extracellular signals to regulate cell growth and survival [164–166]. There are three major subfamilies of MAPK: extracellular signal-regulated kinase (ERK)-1 and -2, stress-activated protein kinase (SAPK)/c-Jun N-terminal kinase (JNK) and p38 MAPK. All three MAPKs have been implicated in regulating cisplatin-induced cell death.

ERK is activated in response to growth factors and mitogens. Cisplatin has been shown to cause activation of ERK in several cell types although there are controversies whether activation of ERK prevents or contributes to cisplatin-induced cell death [167–173]. ERK has been shown to function as a prosurvival protein in ovarian cancer [102, 174], melanoma [175], cervical cancer SiHA [176], human myeloid leukemic [177], and gastric cancer [178] cells. High basal nuclear phospho-ERK2 was associated with cisplatin resistance of ovarian cancer OVCAR-3 cells [179]. Furthermore, nanoparticle-mediated delivery of MEK inhibitor PD98059 enhanced antitumor activity of cisplatin in melanoma-bearing mice [180]. Cisplatin-induced ERK activation precedes p53-mediated DNA damage response since ERK directly phosphorylates p53 causing upregulation of p21, GADD45, and Mdm2 [181]. Thus, activation of ERK may cause cell cycle arrest allowing time for the repair of cisplatin-induced DNA damage via p53. ERK also induced phosphorylation of BAD at Ser112 site in response to cisplatin in ovarian cancer cells, and

inhibition of ERK by PD98059 or mutation of Ser112 to Ala sensitized cells to cisplatin [174]. In SiHA cells, phosphorylation and activation of NF-κB were associated with the prosurvival function of ERK [176]. Glutathione-mediated cisplatin transport and GSTP1 expression also contributed to the antiapoptotic function of ERK in human myeloid leukemic cells [177] and gastric cancer cells [178], respectively. Recently, it has been reported that ovarian cancer cells grown in three-dimensional cultures acquired resistance to anoikis and apoptosis when exposed to clinically relevant concentrations of cisplatin [167]. This resistance was mediated by the ERK1/2 signaling and the PI3K/Akt pathway. ERK signaling was also shown to be activated when stimulated by inducers such as the cigarette smoke-carcinogen NNK [4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone], causing cisplatin resistance [182].

ERK activation was also shown to be required for cisplatin-induced apoptosis in cervical cancer HeLa cells [168, 169, 173], osteosarcoma and neuroblastoma cells [183], testicular germ cell tumors [184], glioma cells [185], renal epithelial cells [186], nasopharyngeal carcinoma cells [187], and human small cell lung cancer cells [188]. Decrease in ERK level/phosphorylation was associated with cisplatin resistance in HeLa cells [168, 173]. Cisplatin-induced activation of p53 was associated with proapoptotic effect of ERK1/2 in B104 cells [189], whereas cisplatin-induced acute renal failure (ARF) in mice was attributed to increase in TNFα gene expression by ERK and activation of caspase-3 [190]. We have found that knockdown of PKCδ attenuates cisplatin-induced ERK activation and apoptosis [173], suggesting that PKCδ acts upstream of ERK1/2 to trigger cisplatin-induced apoptosis.

7.3. Cisplatin and JNK. c-Jun N-terminal kinase or stress-activated protein kinase is activated by various stress stimuli, including DNA damage. The involvement of the JNK pathway in cisplatin-induced apoptosis began when it was seen that cells defective in JNK pathway were resistant to cisplatin [191]. Although both cis and transplatin activated the JNK pathway, the kinetics of JNK activation was distinct [192]. Slow and persistent activation of JNK by cisplatin as opposed to rapid and transient activation of JNK by transplatin may explain the ability of cisplatin to induce cell death. The observation that p73, a proapoptotic member of the p53 family, forms a complex with JNK leading to cisplatin-induced apoptosis, provides a mechanistic basis of how JNK activation leads to cisplatin-induced apoptosis [193]. A mutation in the binding sites of JNK reduced p73-mediated apoptosis. In addition, JNK has been involved in cisplatin-induced cytotoxicity mediated by the latent membrane protein-1 (LMP-1) of the Epstein-Barr virus [190, 194] and phospholipase A2-activating protein (PLAA) [195]. Furthermore, inhibition of TWIST [196], Snail [197], cytokeratin-8 [198], and the RNA-dependent protein kinase (PKR) [199] has been reported to induce JNK activation leading to cisplatin-mediated cytotoxicity. Studies have also implicated activation of JNK pathway following recognition of cisplatin-induced DNA damage by the MMR [121, 200]. JNK and c-Abl were proposed to be signal transducers involved in MMR system that recognizes the cisplatin-DNA adducts and induce cell death [121]. In addition to its role in regulating anticancer activity of cisplatin, JNK pathway has also been implicated in the nephrotoxicity induced by cisplatin. Inhibition of the JNK pathway was cytoprotective restricting renal cell death and inflammation [201]. Recently, the JNK pathway was also shown to mediate cisplatin-induced nephrotoxicity driven by the Toll-like receptor, TLR4 [202].

7.4. Cisplatin and p38 MAPK. The p38 MAPK family is activated by environmental stress and inflammatory cytokines and is an important mediator of cisplatin-induced apoptosis. The activation of this pathway by cisplatin has been seen in different experimental model systems, resulting in a cisplatin-sensitive phenotype [203]. Inhibition of p38 MAPK rendered cells resistant to cisplatin and restimulation of the p38 MAPK along with JNK sensitized cisplatin resistant ovarian cancer 2008/C13* cells by increasing the expression of FasL [204]. Akt2 has been shown to negatively regulate the p38 MAPK pathway by binding to and phosphorylating one of the p38 family members ASK1, resulting in the inhibition of this pathway and rendering the cells resistant to cisplatin [205]. The p38 MAPK pathway was shown to be activated in response to agents such as curcumin which induced apoptosis in cisplatin-resistant ovarian cancer cells [206]. Thus, the activation of p38 MAPK regardless of the upstream signaling pathway seems to be important in mediating cisplatin-induced cytotoxicity. Winograd-Katz and Levitzki identified EGFR as a substrate for p38 MAPK and cisplatin-induced receptor internalization was triggered by p38-mediated phosphorylation of the receptor [207]. p38 MAPK has been shown to mediate its effect via p18(Hamlet), a p38 MAPK-regulated protein, which interacts with p53 and stimulates the transcription of proapoptotic genes PUMA and NOXA to induce apoptosis [208]. Like JNK, p38 MAPK has also been implicated in contributing to nephrotoxicity possibly via TNFα [209, 210]. Thus, the p38 MAPK pathway plays a critical role in regulating cisplatin-induced apoptosis.

7.5. Cisplatin and Akt. Akt belongs to a family of serine/threonine kinases which act downstream of phosphoinositide 3-kinase (PI3K) and plays a critical role in cell survival [211]. Several studies have established the involvement of Akt in contributing to the acquired resistance to cisplatin in several cancers, including ovarian [174, 212], uterine [213], small-cell lung cancer [214], nonsmall-cell lung cancer [215] and hepatoblastoma [216]. Hayakawa et al. first demonstrated that cisplatin-induced DNA damage caused phosphorylation of BAD at Ser136 via Akt and inhibition of Akt sensitized ovarian cancer cells to cisplatin [174]. Asselin et al. provided evidence that the X-linked inhibitor of apoptosis (XIAP) inhibits cisplatin-mediated cell death in cisplatin-sensitive A2780 ovarian cancer cells via phosphorylation and activation of Akt [217]. On the other hand, Dan et al. demonstrated that XIAP is a substrate for Akt and phosphorylation of XIAP by Akt prevents its ubiquitination and degradation in response to cisplatin, suggesting

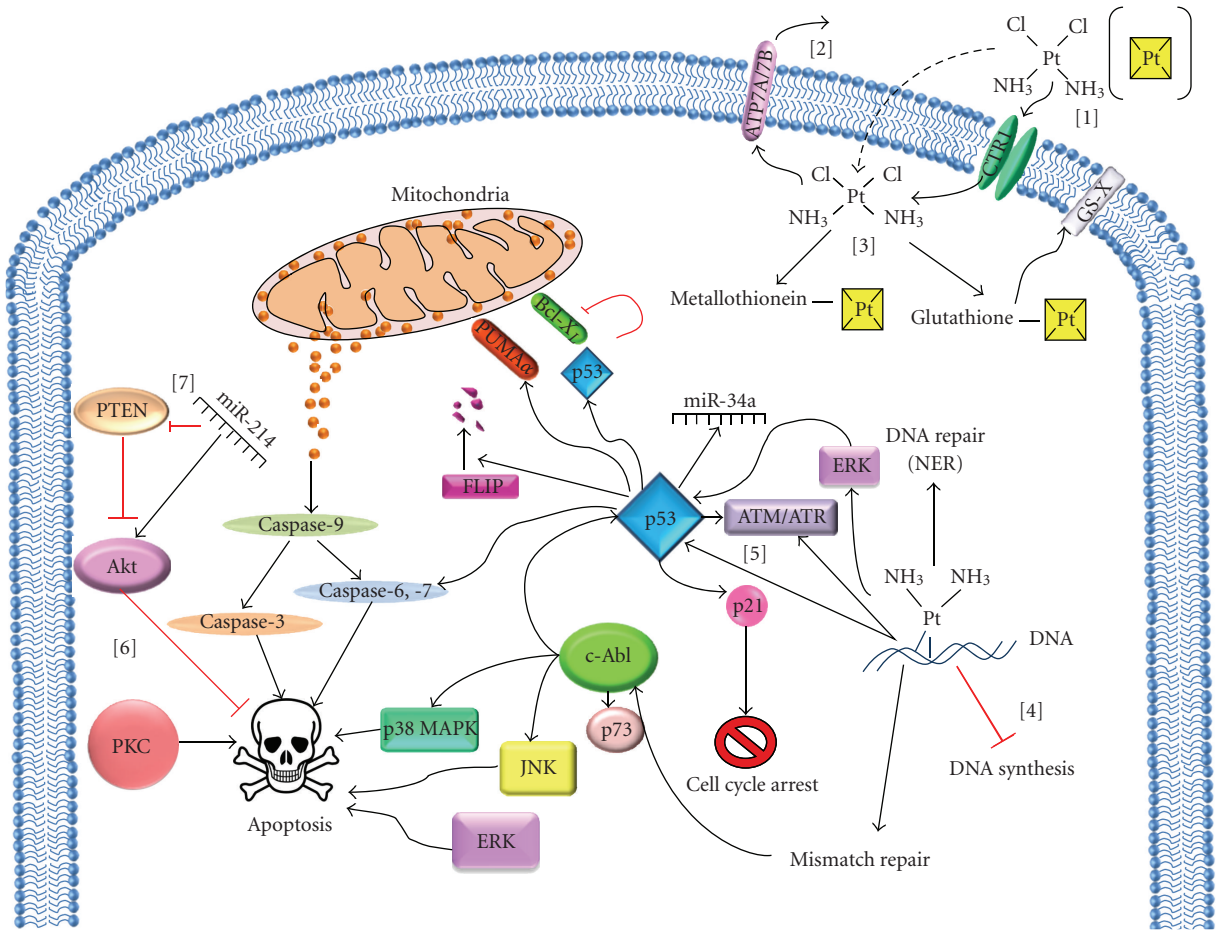

Figure 1: Cellular responses to cisplatin-induced DNA damage. [1] Entry of cisplatin into cells by passive diffusion (indicated by dotted arrows), carrier-mediated transport, employing copper transporter-1 (CTR1). [2] Efflux of cisplatin from the cells by the ATP-dependent transporters, ATP7A and ATP7B. [3] Cisplatin binds to cellular thiols, such as glutathione and metallothionein. The glutathione-cisplatin conjugates are further transported from the cells by the ATP-dependent, GS-X pumps. [4] Once cisplatin interacts with DNA, it stalls cell proliferation by inhibiting DNA synthesis, followed by activation of DNA damage response. [5] Cisplatin-DNA adducts is primarily repaired via the nucleotide excision repair (NER) system and also induces cell-cycle arrest. The DNA damage response is transduced mainly via p53 and c-Abl. Cisplatin-induced DNA damage activates p53, leading to the induction of p21, GADD45, proapoptotic PUMAα, caspase-6, -7, and microRNAs such as miR-34a. p53 also promotes cisplatin-induced apoptosis by binding and inhibiting the antiapoptotic Bcl-xL and also by degradation of FLIP. Cisplatin-DNA adducts activates the mismatch repair system which further activates c-Abl, leading to the activation of JNK and p38 MAPK and stabilization of p73 resulting in apoptosis. [6] Kinases such as PKC, ERK, and Akt are also involved in the regulation of cisplatin-induced cell death. [7] miR-214 promotes cisplatin resistance by downregulating PTEN and activating Akt.

that XIAP promotes cell survival acting downstream of Akt [218]. In small-cell lung cancer cells, the antiapoptotic protein survivin appears to mediate the effect of Akt in protecting against cisplatin-induced cell death [214].

PI3K/Akt inhibitor not only sensitized ovarian cancer cells to cisplatin *in vitro* but also enhanced the antitumor activity of cisplatin in nude mice implanted with Caov-3 human ovarian cancer xenograft [212]. Cisplatin increased p53 and decreased XIAP in cisplatin-sensitive ovarian cancer 2008 cells but not in cisplatin-resistant variant 2008/C13* cells unless Akt was inhibited. The status of p53 also influenced the ability of Akt inhibitors to potentiate cisplatin sensitivity. Ectopic expression of the tumor suppressor PTEN which inhibits PI3K/Akt pathway sensitized cisplatin-resistant ovarian cancer 2008/C13* cells containing wild-type p53 but not in A2780/CP cells containing mutant p53 [105]. It has been suggested that Akt promotes chemoresistance by decreasing p53 phosphorylation and PUMA upregulation [219]. Heat shock protein, HSP27 which is often overexpressed in cisplatin-resistant cells enhanced cisplatin-induced Akt phosphorylation, suggesting that HSP27 may contribute to chemoresistance via the Akt pathway [220]. Among the Akt isoforms, Akt2 has been associated with chemoresistance of ovarian and uterine cancers [205, 213, 221]. However, acquisition of resistance by human lung cancer cells was associated with Akt1 overexpression and gene amplification [222]. Abedini et al. demonstrated that Akt confers cisplatin resistance via inhibition of p53-dependent ubiquitination and degradation of FLIP in response to cisplatin [223]. Claerhout et al. raised

the possibility that autophagy plays an important role in contributing to cisplatin resistance [224]. In a progressive model of cutaneous squamous cell carcinoma cell lines, inhibition of autophagy by 3-methyladenine or by ATG5 knockdown, along with inhibition of Akt enhanced the cytotoxicity of cisplatin [224]. Recently, it has been reported that several microRNAs are deregulated in ovarian cancer and miR-214 promotes cell survival and cisplatin resistance by downregulating PTEN and activating Akt [225]. Thus, Akt/PTEN pathway plays an important role in cisplatin resistance and could be intervened to reverse the resistant phenotype.

8. Conclusion

Despite significant advancements in drug development and molecular-targeted therapy, traditional chemotherapy continues to be the major treatment option. For more than thirty years, cisplatin serves as one of the most important anticancer drugs used clinically. However, cisplatin resistance continues to be the major hurdle in cancer chemotherapy. As depicted in Figure 1, cellular sensitivity to cisplatin is not only regulated by its uptake, efflux or interaction with its target DNA but cellular responses to cisplatin-induced DNA damage also play a major role in deciding the ultimate cell fate. Cells can activate protective responses to inhibit cell cycle progression and repair cisplatin-induced DNA damage. Although extensive DNA damage can induce cell death by apoptosis, several signaling pathways, including Akt, PKC, and MAPKs (e.g., ERK, JNK, and p38 MAPK) can regulate cisplatin-induced apoptosis. The tumor suppressor protein p53 play a critical role in regulating cell cycle arrest, DNA repair and apoptosis. The nonreceptor tyrosine kinase c-Abl can also participate in DNA damage response by activating various MAPKs and interacting with p53 and p73. Recent evidence suggests that microRNAs can also regulate cisplatin sensitivity. Since various signaling pathways regulate cisplatin sensitivity, one way to improve the efficacy of cisplatin is to use it in combination with agents that target the signaling pathways and contribute to cisplatin resistance. Additionally, combining cisplatin with molecular-targeted therapy should lower the dosage of cisplatin currently employed and thus help in alleviating its side effects such as nephrotoxicity. As discussed in this paper, the cellular context has significant impact in deciding the ultimate response to cisplatin and may vary from one patient to another. Thus, the major challenge is to develop individualized therapy options that will be tailor-made to benefit a particular patient. Given the uncertainty with the success of any newly developed drug and the success of cisplatin as a chemotherapeutic agent, this approach may be more feasible and should be actively pursued.

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