Mechanisms of resistance to cisplatin and carboplatin

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Contents

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Abstract

While cisplatin and carboplatin are active versus most common cancers, epithelial malignancies are incurable when metastatic. Even if an initial response occurs, acquired resistance due to mutations and epigenetic events limits efficacy. Resistance may be due to excess of a resistance factor, to saturation of factors required for tumor cell killing, or to mutation or alteration of a factor required for tumor cell killing. Platinum resistance could arise from decreased tumor blood flow, extracellular conditions, reduced platinum uptake, increased efflux, intracellular detoxification by glutathione, etc., decreased binding (e.g., due to high intracellular pH), DNA repair, decreased mismatch repair, defective apoptosis, antiapoptotic factors, effects of several signaling pathways, or presence of quiescent non-cycling cells. In lung cancer, flattening of dose–response curves at higher doses suggests that efficacy is limited by exhaustion of something required for cell killing, and several clinical observations suggest epigenetic events may play a major role in resistance.
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1. Introduction

Cisplatin and carboplatin have broad antitumor activity, but normal tissue toxicity is largely limited to gastrointestinal enterochromaffin cells, kidney convoluted tubules, cochlear hair cells, dorsal root ganglia and megakaryocytes [1], suggesting an epigenetic influence in toxicity. Normal cells have several mechanisms of protection from a noxious environment [2–4] that may also underlie cancer chemotherapy resistance.

2. Platinum resistance

Cisplatin resistance has been studied to a greater extent than has carboplatin resistance. However, in reviewing platinum resistance mechanisms, the overall available data strongly suggest that resistance mechanisms are very similar for cisplatin and carboplatin (although not always identical). In this review, we will make the assumption that the same mechanisms generally apply to both, recognizing that this will not be so in all instances.

For colon and renal cancers, intrinsic resistance limits platinum usefulness. For many other malignancies, some patients initially respond, but acquired resistance then develops. While acquired resistance has been attributed to mutations [5], various clinical [6] and laboratory [7] observations and the rapid induction of resistance with brief drug exposure in vitro [8] and clinically [9,10] suggest epigenetic changes may also be important.

We hypothesized that resistance mechanisms may be regarded in pharmacodynamic terms and that dose–response relationships would reflect the major mechanisms underlying resistance [11]. Resistance may be classified as "active" (due to excess resistance factor, giving a shoulder on a dose–response curve [DRC]) (Fig. 1) versus saturable passive (deficiency of a factor required for drug efficacy, giving a DRC terminal plateau) versus non-saturable passive (due to factor alteration, giving a decreased DRC slope) [11]. Examples of active resistance factors would include efflux pumps, DNA repair systems, anti-apoptotic factors, etc. Examples of factors that might give saturable passive resistance if deficient would include drug uptake or activating systems, obligate targets (e.g., topoisomerase II for topoisomerase II inhibitors), proapoptotic factors or factors that are part of the apoptotic cascade, or cells in a sensitive phase of the cell cycle. Non-small cell lung cancer (NSCLC) DRCs for cisplatin combinations flatten at higher doses, suggesting that efficacy is ultimately limited by saturable passive resistance, i.e., by deficiency of a required factor [12]. A potential example would be the presence of non-cycling cells, in keeping with the relative resistance in vitro of quiescent/slowly proliferating cells [13–16]. Overall, several factors may contribute to resistance (Table 1).

3. "Classical" resistance mechanisms

3.1. Blood flow and drug delivery

Delivery of chemotherapy and oxygen varies with blood flow. Hypoxia reduces efficacy of many agents, but has little impact on cisplatin [17]. With respect to drug delivery, tissue drug concentrations conform to either flow-limited models (varying with blood flow [18]) or to membrane-limited models (not proportional to flow) [19,20]. Against a flow-limited model for cisplatin, concentrations are as high in necrotic as in viable human tumors [21] and cisplatin concentrations

Table 1
Mechanisms of resistance to platinums

Mechanism	Contributing factor		
Impaired blood flow/drug delivery	↑ Tissue pressure[a] ↓ Blood pressure[e]	↑ Plasma fibrinogen[b] ↓ RBC deformability[b]	↑ Blood viscosity[b]
Extracellular matrix/other factors	↑ Tissue pressure[a]/↓ diffusion ↑ Fibronectin	↑ γ-Glutamyltransferase ↑ Type IV collagen	↑ Laminin
Decreased drug uptake	↑ Cell membrane rigidity ↑ NaCl[c] ↑ Extracellular pH ↓ Copper transporter CTR1 ↓ Uptake concurrently of several factors Defective endocytosis/formation of endocytic recycling compartment	↑ Sphingomyelin ↑ KCl[c] ↑ Protein binding ↑ Copper Concurrent ↓ expression several transporters ↓ Small GTPases (rab5, rac1, rhoA) which regulate endocytosis	↑ Cholesterol ↑ Mannitol[c] ↓ CaCl$_2$[c] ↓ γ-Catenin
Increased efflux	↑ Cu transporters ATP7A, -7B ↑ MRP2/cMOAT/GSH-X pump[d] ↑ MVP/LRP[d]	↓ CuCl$_2$[c] ↑ MRP1[d] Abnormal sorting into exosomal pathway	↑ Intracellular pH ↑ p-Glycoprotein[d] ↑ Sequestration intracelluarly
Increased detoxification	↑ GSH ↑ γ-Glutamylcysteine synthase ↑ Glutamate cysteine ligase ↑ Dihydrodiol dehydrogenase	↑ GST[d] ↑ γ-Glutamyltransferase ↑ GSH reductase ↑ Superoxide dismutase	↑ GST-pi/GST-pi SNPs[e] ↑ GSH peroxidase ↑ Catalase ↑ Metallothioneins[d,e]
Decreased drug binding	↑ Proton pumps ↑ In cell cycle G1/ ↓ in G2/M	↑ Intracellular pH ↑ Histone methylation	↑ Extracellular pH
Increased DNA repair	↑ Nucleotide excision repair system (ERCC1 and XPF) Host ERCC1/XPD SNPs[e], ↑ Base excision repair (DNA polymerase-β[d], -zeta, and -eta) ↑ DNA damage recognition protein HMG1	↑ XPA[e] ↑ Topoisomerase-II ↑ Homologous recombination repair	↑ BRCA1[e] ↑ REV1 ↑ DDB2 (damaged-DNA-binding-protein-2
Increased tolerance of DNA damage	↓ DNA postreplicational mismatch repair	↓ hMLH1, hMSH2, hMSH6[d]	↓ Non-homologous end-joining repair
Decreased pro-apoptotic factors	Down-regulation/↓ expression (p53, p53-binding-protein-2, Bax, Fas, caspases 8, 9, other) Mitochondrial abnormalities	↓ Activation (Fas, caspase 9) P53 deletion	P53 mutation (with overexpression of a non-functional protein)[d,e]
Increased apoptosis inhibitors	↑ Bcl-2[d,e] ↑ Survivin ↑ Xiap	↑ Bcl-xL[d,e] Hypoxia (via ↑ Bcl-xL) ↑ IAP-2	↑ Bfl-1/A1 ↑ FLIP ↑ COX-2[d,e]
Altered mitochondria	↑ Fatty acid use for O$_2$ consumption ↓ Membrane potential	↑ Mitochondrial-uncoupling-protein-2	↑ No. mitochondria
Increased chaperones	↑ HSP27[d] ↓ GRP78	↑ HSP90-β	↑ HSP70
Altered cell signaling pathways	↑ E-cadherin ↑ Heregulin/ ↑ p21WAF1/CIP1 ↑ PI3K ↑ MAPK signaling cascade[d] ↑ c-Myc/c-Fos/c-Jun activation ↑ STAT1/STAT3/JAK2 ↑ Protein phosphatases 2A & 4 ↓ p38 kinase activation	↑ EGF/EGFR ↑ Her-2/neu[d] ↑ AKT ↑ p110α ↑ /Mutated ras ↑ PDE2 SRPK1 inactivation ↓ IP3R1	Catenins: ↑ α & β / ↓ γ PTEN loss ↑ mTOR ↑ Hyaluronan-CD44 ↑ c-cot ↑ PKC-iota ↓ SAPK/JNK activation ↓ HGF
Transcription factors, cell cycle related factors, checkpoint kinases, etc.	↑ YB-1 ↑ ZNF143 ↑ Zipper transcriptional factor ↑ NF-kappaB[d] ↓ Chk1 ↓ Telomerase mRNA expression	↑ CTF2 ↑ mtTFA ↑ AP-2 ↑ Cyclin D1 ↓ Chk2 ↓ Telomere length	↑ ATF4 ↑ Ets-1 ↑ SKP2 ↓ Telomerase activity

Table 1 (*Continued*)

Mechanism	Contributing factor		
Gene arrays: differential expression	↑ FN1	↑ TOP2A	↑ LBR
	↑ ASS	↑ COL3A1	↑ STK6
	↑ SGPP1	↑ ITGAE	↑ PCNA
	↑ MDR1	↑ MRP1	↑ MRP2
	↑ CD55	↑ PGK1	↓ Caveolin 1
Proteomic analyses: differential expression	↑ HSP60/HSP90/heat-shock cognate 71 kDa protein	↑ Calmodulin	↑ Calumenin
	↑ Peroxiredoxins PRX 2/PRX 6	↑ GST	↑14-3-3
	↑ Voltage-dependent anion-selective channel-1		
Miscellaneous	↑ Ribosomal proteins RPS13, RPL23	Altered sphingolipid pathway	Altered ganglioside expression
	Chromosomal abnormalities	↑ Splicing factor SPF45	↑ Serum LDH[d,e]
	↑ Glucose utilization[f]	↑ Lactate production[f]	↑ LDH-5[e,f]
	↑ Golgi apparatus	↓ Microsatellite D6S1581	↓ Pyruvate kinase M2

[a] Paradoxically associated with improved cisplatin efficacy and patient survival.

[b] Thought to be important for drugs in general, but not directly tested with platinums.

[c] Alter platinum cellular uptake and efficacy when added in vitro.

[d] Effect not seen consistently across all studies, or opposite effect seen in some studies.

[e] Demonstrated in clinical studies.

[f] Despite cells with low intracellular and extracellular pH having decreased platinum efflux and increased platinum uptake, binding and efficacy.

in human autopsy tissues do not correlate with organ blood flow rates [22]. Human tumor cisplatin concentrations do vary with pulse and blood pressure [23], with metastatic site [23], and with tumor type [21,23].

Since blood flow autoregulation is defective in tumors, blood pressure fluctuations have greater impact on flow to tumors than to normal tissues [24], and agents that alter blood pressure may selectively alter tumor blood flow/drug delivery [24–26]. Decreased red blood cell deformability, high fibrinogen levels, etc. may reduce tumor blood flow by increasing blood viscosity [27,28], while agents that reduce blood viscosity (e.g., pentoxifylline, mannitol or fibrinolytics
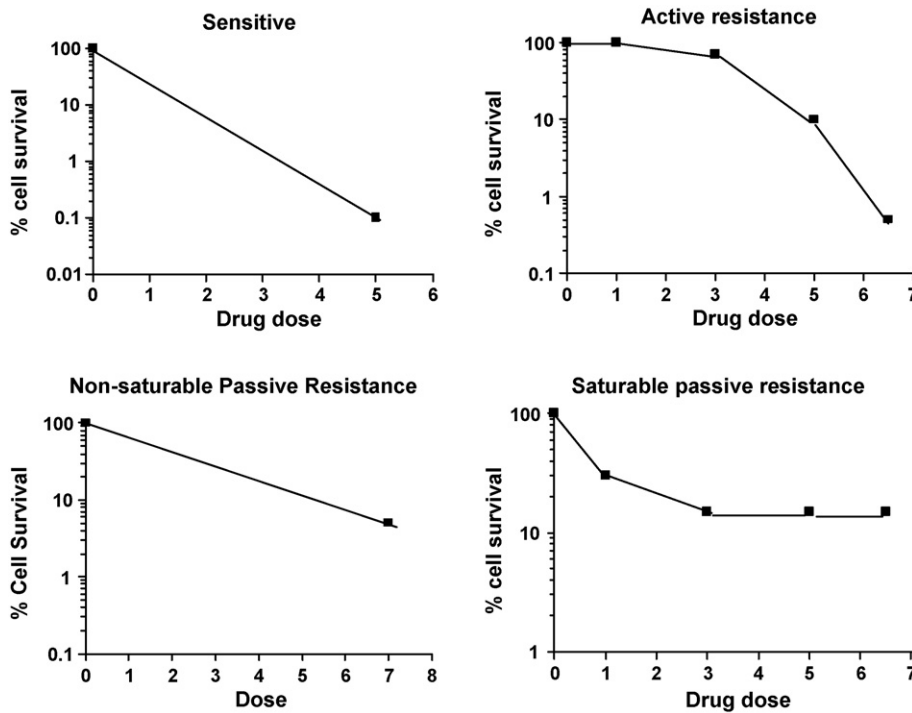

Fig. 1. Dose–response relationships and proposed resistance mechanisms. We hypothesize that if log % cell survival is plotted vs. drug dose, excess of a resistance factor ("active resistance") would give a shoulder on the dose–response curve (analogous to competitive inhibition of drug effect), mutation or alteration of a factor such as a target or drug transport or activating system, etc. ("non-saturable passive resistance") would decrease the slope of the curve (analogous to decreased affinity of a drug for its receptor), and deficiency of a factor required for cell killing ("saturable passive resistance") would give a terminal plateau on the dose–response curve (analogous to non-competitive inhibition of drug effect).

[27,29–31]) might increase tumor blood flow and drug delivery. While both blood flow [32] and drug diffusion through interstitium from vessel to tumor cell [33] may be impeded by the abnormally high tissue pressures in tumors, higher interstitial fluid pressures may nevertheless be associated with increased cisplatin efficacy and prolonged patient survival [34]. Overall, it is unknown to what extent tissue pressure and tumor blood flow affect platinum activity clinically.

3.2. Extracellular environment

Cisplatin-induced apoptosis is reduced in the presence of the extracellular matrix proteins fibronectin, type IV collagen and laminin that may bind tumor cells [35], and extracellular gamma-glutamyltransferase (GGT) may cleave glutathione to yield thiol groups that bind and inactivate cisplatin and other electrophilic drugs [36]. The impact of these factors in the clinic remains unknown.

Unlike tumor intracellular pH (which is neutral-to-alkaline) [37], tumor extracellular pH is often acidic [37,38]. A pH gradient with extracellular pH < intracellular pH favors uptake of weak acids [37], and cisplatin uptake is markedly increased at low extracellular pH [39]. Hence, diet could potentially impact cisplatin efficacy, as tumor extracellular pH is increased by bicarbonate [40] and lowered by glucose administration [41,42]. One might speculate that some of the broad efficacy and favorable therapeutic index for the platinums may be due in part to the relatively greater acidity in many tumors compared to most normal tissues.

Other agents could also potentially have an impact. For example, mannitol and NaCl, both of which are used to decrease cisplatin nephrotoxicity, decrease cisplatin uptake and cytotoxicity in vitro [43,44], as does KCl [43,44], while $CaCl_2$ and $CuCl_2$ may increase net cisplatin accumulation and cytotoxicity [44].

Binding of drug to proteins either in plasma or the interstitium also could contribute to resistance. Protein-bound platinum is much less cytotoxic than is free cisplatin [45,46], with substantially reduced uptake into cells [46] and tissues [47]. Cisplatin binds irreversibly [48] to plasma proteins, with a half-life for protein binding of about 2 h [46]. Carboplatin takes substantially longer to bind to protein than does cisplatin [49–51].

3.3. Drug uptake

Many resistant cell lines have reduced cisplatin accumulation [52–54]. Cisplatin cellular uptake is not saturable with dose, but is altered by metabolic inhibitors [44,54] which do not affect efflux [55]. While some studies found that cell membrane fluidity (which could potentially alter either drug passive diffusion or activity of membrane transport systems) did not correlate with cisplatin uptake [56], others suggested that resistant lines with reduced uptake have rigid cell membranes [57,58] with high sphingomyelin and cholesterol content [58], and sphingolipid pathway modu-

lation [59] and cholesterol depletion [60] increase cellular platinum uptake and efficacy. Cisplatin resistance may also be associated with altered ganglioside expression [61].

The copper transporter CTR1 contributes to platinum cellular uptake [62–66], and CTR1-deficient cells are cisplatin-resistant [63]. Copper transporters undergo rapid cytoplasmic internalization after cisplatin exposure, reducing transporter surface expression and limiting further cisplatin uptake [63,66].

Reduced cisplatin uptake may be associated with a broad reduction in uptake of several factors, including folates, epidermal growth factor (EGF), iron, glucose, etc., in conjunction with downregulation of various transporters, defective endocytosis, and downregulation of the small GTPases rab5, rac1, and rhoA which regulate endocytosis, and this may be reversed via DNA demethylation with reactivation of silenced genes [67]. Microtubule alterations with defective formation of the endocytic recycling compartment may lead to cisplatin resistance and reduced uptake of cisplatin and other molecules [68]. The extent to which reduced transport and uptake contributes to platinum resistance in the clinic remains unclear. However, note that the flat dose–response curve seen with platinums in non-small cell lung cancer could hypothetically result from saturation of drug uptake systems.

3.4. Drug efflux

Resistance may also be associated with increased cisplatin efflux from cells [15,69] or from nucleus into cytoplasm [70]. The copper-transporting P-type adenosine triphosphatases ATP7A and ATP7B have been implicated in platinum efflux and resistance [64,71–76]. Copper competes with cisplatin for uptake into cells, but also reduces cisplatin efflux [55], and may increase cisplatin net accumulation and cytotoxicity [44]. ATP7B overexpression is associated with poor outcome in cisplatin-treated patients with esophageal cancers [73] and squamous cell cancers of the head and neck (SCCHN) [74], suggesting that ATP7B-associated platinum efflux could potentially contribute to clinical platinum resistance.

Other pumps that may also play a role in cisplatin resistance (±enhanced efflux) include the MRP2 (multidrug-resistance-associated-protein-2)/cMOAT (canalicular Multispecific Organic Anion Transporter)/glutathione-X-conjugate pump [75,77–82], MRP1 [83,84], p-glycoprotein [80,82,84–87], and major vault/lung resistance-related protein (MVP/LRP) [70,82,88–90], although there have also been negative studies for MRP1 [91], MRP2 [92], p-glycoprotein [91,93], and LRP [84,91]. In ovarian cancer (OC) cells, LRP down-regulation reversed resistance, increased cellular cisplatin accumulation, increased cisplatin in isolated nuclei, and decreased cisplatin efflux from nuclei [70].

Resistance has also been associated with abnormal sorting of some lysosomal proteins and cisplatin transporters

into an exosomal pathway [75], and with drug sequestration in subcellular organelles such as melanosomes, with significantly reduced drug nuclear localization and with increased extracellular transport of melanosomes containing cisplatin [94].

Resistant lines with increased cisplatin efflux also may have increased intracellular pH [15]. Intracellularly, cisplatin's chlorides are replaced by neutral hydroxy or highly reactive positively charged aqua groups, with the pK_a for the interconversion between chloro-hydroxy and chloro-aqua species being 6.56 [95]. Hence, if intracellular pH is high, a higher proportion of drug may be in the uncharged chloro-hydroxy form, with increased passive efflux of this form. Again, clinical importance of each of these different efflux mechanisms remains uncertain.

3.5. Drug detoxification

Increased glutathione (GSH) may cause resistance [96–100] by binding/inactivating cisplatin, enhancing DNA repair, or reducing cisplatin-induced oxidative stress [53]. Glutathione-*S*-transferase (GST) [14,86,100–102], particularly GST-pi [103–109] or specific GST-pi polymorphisms [109], may augment resistance by catalyzing GSH-drug binding, although not all studies agree [96,97]. Clinically, GST-pi gene amplification [104], immunostaining [105], host gene polymorphisms [101], and plasma levels [106] correlated with cisplatin resistance clinically, suggesting that platinum detoxification by GSH and GST may be clinically important.

Other GSH-related enzymes such as gamma-glutamyl-cysteine synthetase [102], gamma-glutamyltransferase [36], glutamate cysteine ligase [110], GSH peroxidase [99], GSH reductase [102,111], and catalase [87,99] have also been linked to cisplatin resistance, as have the antioxidants superoxide dismutase [87,112,113] and dihydrodiol dehydrogenase [114] in preclinical systems.

Metallothioneins (sulfur-containing proteins involved in zinc homeostasis) have been associated with resistance to cisplatin in some studies [87,96,108,115–118] (but not others [97]), presumably through drug binding, and correlated with clinical cisplatin resistance in hepatocellular carcinomas [117] and NSCLC [118], again suggesting its clinical relevance as a platinum resistance mechanism. Zinc upregulates metallothionein expression and decreases cisplatin efficacy [119].

3.6. Drug binding

As noted above, intracellularly cisplatin's chlorides are replaced by neutral hydroxy or highly reactive positively charged aqua groups [95]. Chloro-aquated platinum accounts for most DNA binding [120]. Intrastrand and interstrand DNA crosslinks are responsible for cell killing [121]. DNA adduct levels in lymphocytes correlate with those in tumor [122] and with platinum efficacy [122–127], although not in all studies [122,128,129]. Platinum–DNA adducts are found primarily in nuclear high-density chromatin loci and in mitochondria, with highest adduct levels in dividing cell [130]. Cisplatin cytotoxicity and DNA binding are highest with cell exposure during G1 and lowest during G2/M [131]. Reducing histone methylation relaxes condensed chromatin, increases cisplatin access to DNA, increases DNA–platinum adduct formation, and augments cisplatin efficacy [132].

Decreased DNA adduct formation and cisplatin resistance may occur despite high cellular concentrations [52]. Cisplatin is most effective at low intracellular [133] and extracellular [39] pH, and pH was significantly increased in cisplatin-resistant cells with reduced DNA binding [15,134]. Cisplatin DNA binding is markedly increased in acidic conditions [134]. Cisplatin-resistant lines had upregulation of expression of proton pumps [134], and proton pump inhibitors augment cisplatin retention [135] and efficacy [134,135], although results varied between lines [136]. Intracellular pH is lowest during G1 and highest during G2/M, in keeping with cisplatin's phase-specific relative DNA binding and cytotoxicity [131].

The major determinants of intracellular pH were H^+-linked monocarboxylate transporters in melanoma cells versus the Na^+/H^+ exchanger in normal tissues, suggesting that monocarboxylate transporter inhibitors might selectively sensitize tumors [137]. In other systems, the lactate-/H^+ symporter was the most active exchanger regulating tumor cell pH under aerobic conditions, while in hypoxia, lactate extrusion is reduced and a major factor in maintaining normal cytosolic pH despite an acidic extracellular environment may be enhanced sequestration of protons into acidic cellular vesicles [138]. Tumor cell pH may also correlate with nucleoside triphosphate/inorganic phosphate ratios [139].

Anaerobic glycolysis and other processes drive tumor acid production [140]. Lowering extracellular pH markedly increases cisplatin uptake and DNA binding, and also lowers intracellular pH [39]. In vivo, intravenous glucose administration lowers tumor extracellular pH [41,42], while oral bicarbonate administration raises it [40]. However, despite low pH enhancing cisplatin uptake and binding and reducing efflux, glucose utilization and lactate production may be increased in resistant lines [15]. Furthermore, tumor expression of the HIF-1 regulated isoenzyme lactate dehydrogenase (LDH)-5 (the LDH isoenzyme most important in anaerobic glycolysis and in pyruvate–lactate conversion) predicts poor prognosis [141], while the LDH isoenzyme most efficient at converting lactate to pyruvate under aerobic conditions is associated with *increased cisplatin sensitivity* [142]. High serum LDH level is associated with poor prognosis in many [143–155] but not all [156–158] platinum-treated malignancies. Expression of pyruvate kinase M2 (another key glycolytic pathway enzyme) was reduced in resistant cells [159]. In summary, there is substantial preclinical evidence suggesting that reduced extracellular and intracellular pH may be associated with platinum uptake, binding and cytotoxicity, but its importance clinically has not yet been adequately assessed, and high LDH expression (which might be expected

to be associated with reduced tumor pH) is often associated with poor outcome in patients with platinum-treated malignancies.

3.7. DNA repair

Cisplatin is effective versus testicular carcinoma, which has a particularly low capacity to repair platinum-induced DNA damage [160]. Cisplatin is most efficiently removed from transcribed areas within DNA [161] and gene-specific repair efficiency of cross-links correlates with resistance [162]. Platinum damage is repaired primarily by the nucleotide excision repair (NER) system (particularly ERCC1 and ERCC1/XPF) and the related genes XPA and BRCA1 [163,164]. ERCC1 overexpression (without gene amplification [165]) is associated with reduced platinum-based therapy efficacy in both OC [166] and NSCLC [111,118,167], and response [168] or survival [107] varies with host genotype ERCC1 polymorphisms. However, ERCC1 is involved mainly in removal of interstrand cross-links rather than therapeutically important intrastrand cross-links [53].

Polymorphisms of XPD (involved in the NER transcription-coupled repair pathway) conferring reduced repair capacity are associated with increased platinum sensitivity [169], and are associated with a trend towards improved outcome in some NSCLC studies [170], but not others [107]. In OC, cisplatin resistance is associated with enhanced expression of XPA (but not with XPA gene mutation or amplification [171]), and with upregulation of expression of the Fanconi Anemia/BRCA pathway [172,173]. BRCA1 mutation augments lymphocyte sensitivity to cisplatin [174], and in NSCLC patients treated with neoadjuvant cisplatin/gemcitabine, low tumor BRCA1 mRNA levels predicted better survival [113].

The base excision repair enzyme DNA polymerase-β is overexpressed in several cisplatin-resistant cell lines demonstrating translesion synthesis across platinated crosslinks [175–177]. Incorporation of incorrect bases is frequent during platinum adduct repair by DNA polymerase-β [177]. Cell transfection with DNA polymerase-β genes increases cisplatin resistance [178], while DNA polymerase-β antagonists [179,180] increase cisplatin efficacy, although not in all studies [181]. AP-2 transcription factors which are modulated by protein kinase A (PKA) and regulate genes for DNA polymerase-β and metallothioneins also are associated with cisplatin resistance [182].

DNA polymerase-zeta is associated with cisplatin resistance [183], and may enable mutagenic bypass of replication-blocking DNA adducts [184], as may DNA polymerase-eta [185]. The bypass replication by DNA polymerase-eta may be more efficient [177] and less error-prone [177,186] than with DNA polymerase-β. REV1, which interacts with Y-type DNA polymerases and DNA polymerase-zeta to bypass many types of adducts that block the replicative DNA polymerases also confers cisplatin resis-

tance [187]. Cytarabine, which inhibits DNA polymerase-α [188,189], is synergistic with cisplatin [190].

Topoisomerase-II [191] and homologous recombination repair [179,192] may also increase platinum DNA damage repair, while non-homologous end-joining repair may enhance platinum efficacy [193]. Cisplatin resistance has also been associated with overexpression of the DNA damage recognition protein HMG1 (which may shield DNA adducts from repair) [194] and of damaged-DNA-binding-protein-2 (DDB2) (which is involved in UV damage repair) [195]. The O^6-alkylguanine-DNA-alkyltransferase repair system does not confer cisplatin resistance [196,197].

Cisplatin adduct formation is greater and repair less on mitochondrial DNA versus genomic DNA [198], although the significance of cisplatin mitochondrial DNA binding remains unknown.

Overall, there are clinical data that support a role for components of the NER pathway in platinum resistance. While there is preclinical evidence of a role for various DNA polymerases, topoisomerase II and homologous recombination repair in platinum resistance, there is not yet clinical information available on the role of these DNA repair systems.

3.8. Decreased DNA mismatch repair

DNA postreplicational mismatch repair (MMR)-mediated processing of platinum adducts results in apoptosis and *increased* platinum sensitivity [199]. Cells deficient in MMR [199–201] or with reduced nuclear content of the MMR proteins hMLH1, hMSH2 or hMSH6 [202] paradoxically have increased cisplatin resistance and reduced apoptosis [203], although not in all studies [204]. An intact c-Abl and p73 system may be required for MMR to enhance apoptosis, and cells lacking p73 expression after cisplatin exposure may be resistant [205]. DNA polymerase-zeta may be required for the resistance from MMR loss, suggesting that resistance is mediated by enhanced mutagenic translesion synthesis [206]. Concurrent p53 loss also enhances resistance development [206]. From a clinical perspective, hMLH1 gene methylation and down-regulation is common in treated germ cell tumors [207], suggesting that there may in fact be a clinical role for deficient DNA mismatch repair in platinum resistance.

3.9. Reduced apoptotic response

Several genes regulating DNA damage, apoptosis and survival signaling may contribute to resistance [208]. Cisplatin may induce apoptosis through the Fas/Fas ligand signaling complex (with activation of caspase 8, then caspase 3), or by mitochondrial cytochrome-c release [209]. In the presence of ATP and cytochrome-c, apoptotic-protease-activating-factor-1 (Apaf-1) activates caspase 9, with subsequent caspase 3 activation [209]. Cisplatin may also kill via a caspase-3 independent apoptotic pathway, by a defective apoptotic pathway or by necrosis [209].

Defective apoptosis may contribute to resistance to both p53-dependent and -independent cisplatin cytotoxicity [210]. P53 down-regulation may confer resistance, possibly by over-expression of the negative feedback regulator Mdm2, with or without downregulation of p14^{ARF} (which moderates Mdm2) [53]. Resistance has also been associated with reduced p53-binding-protein-2 expression [211].

Cells with p53 deletions [212] or mutations [213] are often resistant to cisplatin. Cisplatin resistance has been associated with p53 mutation *in vitro* in OC [214] and SCCHN [215] cell lines, and clinically in germ cell tumors [216] and SCCHNs [106,217].

p53 mutation is generally associated with protein overexpression, but mutant protein lacks normal tumor suppressor function [218]. p53 overexpression is associated with poor outcome in platinum-treated OC [219] and NSCLC [118,220] patients. However, this is not seen in all studies [155], and glioma cells with mutant p53 paradoxically had enhanced cisplatin-induced apoptosis, while wild-type variants instead responded with G2-M arrest [221].

Caspases 3, 8, and 9 are important in cisplatin-induced apoptosis [53]. A cisplatin-resistant line had global down-regulation of caspase and Bax expression, but increased Bcl-2 [222]. Loss of caspase 8 pathway was associated with cisplatin resistance in a SCCHN cell line [223]. Decreased CD95 (Fas) expression or pathway activation after cisplatin may lead to inhibition of activation of caspases 3 and 8 [53], and was associated with cisplatin resistance in germ cell tumors [224] and OC cells [14]. Decreased cisplatin caspase 9 activation was noted in cells with normal mitochondrial cytochrome-c release and normal Bcl-2 and Bcl-XL expression [225]. Cisplatin-resistant cells have also been reported with abnormal mitochondrial membrane potential, intracellular distribution, or structure, and with up-regulation of cytochrome-c in the mitochondria in response to cisplatin rather than release into the cytoplasm [226].

Overall, there is preclinical evidence of an association of platinum resistance with abnormalities of a variety of apoptotic factors, but to date this has only been documented clinically for p53.

3.10. Apoptosis inhibitors

Apoptosis may be inhibited by overexpression of Xiap (X-linked inhibitor of apoptosis protein) and its interaction with the PI3-K/Akt pathway [227]. Overexpression of Xiap and IAP-2 correlated with cisplatin resistance in some cell lines [228], down-regulating Xiap increased cisplatin sensitivity, caspase-3 activity and apoptosis in resistant ovarian [229] and prostate cancer cells [230], and cell transfection with hRFI (a Ring Finger domain highly homologous to XIAP) induced cisplatin resistance and inactivation of caspase-3 [231]. Cell line overexpression of survivin also correlates with cisplatin resistance [228,232], and survivin antisense oligonucleotides augment cisplatin-induced apoptosis [233].

Bcl-2 [14,234,235] or Bcl-xL [235–237] overexpression (with no change in BAX or Bcl-Xs, but with marked down-regulation of caspase-3 expression [238]) is often (but not always [53]) associated with cisplatin resistance, and was associated with decreased response [239] or disease-free survival [237] in OC patients. Hypoxia increases Bcl-XL expression and resistance to cisplatin [236], while Bcl-2 or Bcl-XL antagonists augment cisplatin efficacy [233,236]. Cisplatin generation of reactive oxygen species causes dephosphorylation and degradation of Bcl-2, while nitric oxide (NO) induces its S-nitrosylation, inhibiting its ubiquitination and upregulating Bcl-2 expression. NO synthase activity and NO production correlate with resistance in NSCLC cells [240].

Overexpression of ribosomal proteins (RP) S13 and RPL23 in a resistant cell line increased Bcl-2 expression, the Bcl-2/Bax ratio, GST activity and intracellular GSH content [241]. Resistant cells also may overexpress the Bcl-2-related protein Bfl-1/A1, mediated by NF-kappaB [242].

Other resistant OC lines had increased expression of Fas-associated death domain-like interleukin-1beta-converting enzyme-like inhibitory protein (FLIP) [243]. Cisplatin decreased FLIP and induced caspase-8 and caspase-3 cleavage and apoptosis in cisplatin-sensitive but non-resistant cells. FLIP downregulation in chemoresistant cells increased cisplatin-induced apoptosis [243].

Hence, several apoptosis inhibitors have been associated with platinum resistance in preclinical systems, with clinical evidence of an association of bcl-2 and bcl-xL with resistance.

4. Newer molecular factors linked to platinum resistance

There are also several new molecular factors that have been linked to platinum resistance. With only a few exceptions, the effect on platinum efficacy has to date been assessed only in vitro, with little information on their impact on resistance in xenograft models or clinically. The extent to which they may also mediate resistance to other unrelated chemotherapy agents is also unclear, as is their potential impact on cross-resistance and on synergism versus antagonism of cisplatin and carboplatin with other agents. For most of these new factors, it is also not yet known whether their apparent ability to counteract platinum efficacy is due to counteracting a specific effect of the chemotherapy agent or whether it is due instead to a more non-specific ability to block cell death/promote cell survival and growth. However, these potential resistance factors are of substantial interest since inhibitors of several of these are currently under development and may eventually prove useful, either as therapy in their own right or else as a means of reversing platinum resistance. Ultimately, inhibitors of these factors will only prove useful if they can reverse chemotherapy resistance in tumor without substantially increasing normal tissue toxicity, and their impact on chemotherapy toxi-

city to normal tissues remains largely undefined at this time.

4.1. Cyclooxygenase-2 (COX-2)

In preclinical studies, cisplatin treatment augmented tumor cell COX-2 expression [244] and cisplatin resistance was induced by COX-2 overexpression [83]. COX-2 inhibitors decreased bcl-2 expression [245] and potentiated cisplatin efficacy in some preclinical studies [83,245,246], but reduced efficacy in others [247]. Clinically, high COX-2 expression was associated with reduced platinum-based therapy efficacy in esophageal [248,249], bladder [250], cervical [251,252] and ovarian [253] cancers, but not in NSCLC [254]. The fact that a link is seen between therapy efficacy and COX-2 expression clinically makes the assessment of COX-2 inhibitors a particularly interesting focus for further research.

4.2. Heat shock proteins (HSP)

HSP27 overexpression [255–257] or gene transfection [256–258] increased cisplatin resistance in cell lines, although not consistently [259,260]. Growing cells to confluence increased HSP27 expression [257]. HSP90-β [261] and HSP70 [256] also may augment cisplatin resistance, and cisplatin treatment increases HSP70 expression in vitro [262]. On the other hand, glucose-regulated-stress-protein-78 (GRP78) overexpression was associated with increased cisplatin sensitivity in colon cancer cell lines [263]. HSP inhibitors are currently undergoing clinical trials, but little is known regarding the role of HSP in clinical resistance, and it remains unknown whether HSP inhibitors will prove useful.

4.3. Cell signaling pathways & molecules

Several signaling pathways and transcription factors may augment cisplatin resistance by promoting cell survival [264]:

4.3.1. Cadherins/catenins

E-cadherin expression is associated with cisplatin resistance in vitro [14,265], as is increased expression of epidermal growth factor receptors (EGFR) and α- and β-catenins [14]. As with HSP, it remains unknown whether E-cadherin plays a role in clinical platinum resistance. However, this area is of interest since EGFR antagonists may be particularly effective against lung cancer cells expressing E-cadherin [266], raising the possibility that E-cadherin expression may eventually help guide the decision whether to treat a lung cancer patient with a platinum-based regimen versus an EGFR inhibitor.

Cisplatin exposure results in proteolysis of γ-catenin, with loss of γ-catenin from adherens plaques and rapid reduction in uptake of subsequent carboplatin in vitro. Cell transfection with γ-catenin increased cisplatin sensitivity [267].

4.3.2. EGF family

Possibly linked to the E-cadherin effect is the fact that EGFR inhibition increased cisplatin sensitivity in NSCLC [268] and nasopharyngeal cancer cell lines [269]. Induction of tumor cell migration by chemotaxis to EGF up-regulates anti-apoptotic genes, down-regulates pro-apoptotic genes, and decreases cisplatin-induced apoptosis in vitro [270]. The related growth factor heregulin modulates expression of p21WAF1/CIP1, a resistance-promoting mediator of DNA repair. Cell lines overexpressing heregulin demonstrate constitutive hyperactivation of Her-2/neu, activation of down-stream PI-3K/AKT and MAPK signaling cascades, up-regulation of p21WAF1/CIP1 expression, nuclear accumulation of p21WAF1/CIP1 [271] and cisplatin resistance [271,272] that may be reversed by trastuzumab [272]. However, in other lines, Her-2/neu over-expression enhanced cisplatin sensitivity instead of resistance [273], and there are conflicting data on the role of the MAPK pathway in cisplatin resistance [53].

Despite the augmentation of cell line sensitivity to cisplatin by EGFR inhibitors, administration of EGFR inhibitors concurrently with platinum-based regimens has not proven useful clinically in NSCLC [274–276]. It has been postulated that inhibition of cell growth by the EGFR inhibitor may render tumor cells resistant to chemotherapy [277], and trials are now underway giving these therapies sequentially rather than concurrently.

4.3.3. PTEN/PI3K/AKT

PI3K inhibitors enhanced cisplatin efficacy in resistant lines [278] and OC xenograft models [279], while SiRNA knockdown of PTEN and the expression of active p110α blocked cisplatin-induced apoptosis and increased resistance [278]. Xiap may inhibit apoptosis through its interaction with the PI3K/Akt pathway [227], and up-regulation of the PI3K/Akt pathway by Her-2/neu may lead to down-regulation of p53 expression and inactivation of the pro-apoptotic proteins Bad and procaspase 9 [53]. Cells expressing Akt1 [280] or Akt2 and Akt3 [281] display cisplatin resistance, with threshold modulation for several apoptotic pathways, increased Bcl-x(L) expression and delayed p53 activation [280]. Akt knockout reduces resistance [281]. Also, inhibition by rapamycin of mTOR (which acts downstream of PI3K/Akt) enhanced carboplatin-induced apoptosis in breast cancer cells [282]. There remains little knowledge about the importance of this pathway in clinical platinum resistance, but early clinical trials are underway combining chemotherapy with inhibitors of mTOR (a signaling molecule which is downstream from AKT).

4.3.4. Hyaluronan-CD44

Hyaluronan is an extracellular matrix ligand for the transmembrane receptor CD44, which acts through mul-

tiple signaling pathways. Hyaluronan-CD44 promotes phospholipase-C calcium signaling and cisplatin resistance in SCCHN [283,284]. Nothing is yet known about its clinical importance in platinum resisance.

4.3.5. IP3R1

A cisplatin-resistant bladder cancer line had reduced expression of the endoplasmic reticulum membrane protein IP3R1 (inositol-1,4,5-trisphosphate-receptor-type1) [285]. IP3R1 suppression in sensitive variants decreased apoptosis and cisplatin sensitivity, while overexpression of IP3R1 in resistant cells increased apoptosis and cisplatin sensitivity [285]. Again, clinical data are lacking.

4.3.6. SRPK1

Inactivation of serine/arginine-rich protein-specific kinase 1 (SRPK1) induces cisplatin resistance [286]. In clinical studies, SRPK1 expression was found to be high in testicular tissues, and was lower in resistant than in sensitive germ cell tumors [286].

4.3.7. Ras

Cells with ras mutation [287] or overexpression or with H-ras or c-cot gene transfection [288] may be resistant, with reduced cisplatin uptake [287], increased metallothionein [287], ERCC1 induction [289], and enhanced DNA repair [182]. The clinical importance of ras in platinum resistance remains uncertain.

4.3.8. C-myc, c-Fos, c-Jun, SAPK/JNK

C-Myc, c-Fos and c-Jun are activated by the MAPK pathway, and may be overexpressed in cisplatin resistance [53]. The c-fos/AP-1 complex turns on other genes in response to DNA damage [182]. Cisplatin induces c-Jun and AP-1 activity [290], and cell transfection with c-jun increases cellular GSH and cisplatin resistance [291]. On the other hand, attenuated MAPK signaling may be associated with cisplatin resistance in some cell lines, possibly due to decreased activation of stress-activated protein kinase/c-Jun N-terminal kinase (SAPK/JNK) and p38 kinase [290]. Cisplatin-induced activation of SAPK/JNK [290,292] and p38 kinase [290] is significantly decreased in resistant lines, and inhibition of JNK [290,292] or p38 kinase [290] attenuates cisplatin-induced apoptosis. JNK pathway stimulation activates c-Jun and sensitizes resistant cells to cisplatin [292].

4.3.9. STATs

OC gene arrays revealed a significant association of STAT1 expression with cisplatin resistance in cell lines [293]. Cell transfection with Stat1 cDNA induced cisplatin resistance, but a Jak/Stat inhibitor failed to augment sensitivity. STAT3 (involved in signal transduction activated by various growth factors and cytokines) is overexpressed in some cisplatin-resistant cell lines [294], and may sup-

press the apoptotic pathway in cisplatin-resistant NSCLC cells [295].

4.3.10. JAK

Addition of erythropoietin to tumor cells induced cisplatin resistance that was reversed by JAK2 inhibition, suggesting erythropoeitin-induced resistance is JAK2-dependent [296].

4.3.11. Protein kinase C (PKC)

In human OC cell lines, PKCα had no role in cisplatin resistance [297], but PKC-iota inhibition sensitized glioblastoma cells to cisplatin by increasing p38 MAP kinase expression [298].

4.3.12. Protein phosphatases 2A and 4

Protein phosphatase-2A [299] and -4 increase cisplatin resistance [300]. Hepatocyte growth factor (HGF) enhances OC cell killing by cisplatin, possibly by up-regulating p38 MAPK activity and down-regulating protein phosphatase-2A [299]. Protein phosphatase-4 regulates several cellular functions and signaling pathways, including NF-kappaB and mTOR pathways, and decreases histone deacetylase activity [300]. Again, the clinical significance of these observations remains uncertain.

4.4. cAMP–phosphodiesterase 2

The gene PDE2, encoding cAMP–phosphodiesterase-2, may induce resistance by increasing tolerance of cisplatin-induced DNA lesions [301].

4.5. Cell-cycle related factors

S-phase-kinase-associated-protein-2 (SKP2) controls stability of cell cycle-related proteins. SKP2 overexpression reduced expression of p27Kip1, cyclin E, and p21Cip1, increased S-phase cells, and increased cisplatin resistance, while SKP2 down-regulation increased sensitivity in vitro [302]. Cyclin D1 overexpression augmented pancreatic cancer cell chemoresistance both by promoting cell proliferation and by inhibiting drug-induced apoptosis in association with upregulation of NF-kappaB activity [303]. However, while restoration of wild-type p16 to melanoma cell lines restored radiation sensitivity, it had no impact on cisplatin sensitivity [304].

4.6. Checkpoints

Checkpoint-kinase-2 (Chk2) is a critical kinase governing the cell cycle checkpoint, DNA damage repair, and cell apoptosis in response to DNA damaging signals. Cisplatin induces Chk2 degradation through the ubiquitin-proteasome pathway, and Chk2 expression is decreased in cisplatin-resistant OC cells [305]. Chk1 may also be important in the cellular response to cisplatin [306]. Cisplatin-induced apoptosis in gastric cancer cells is also reduced

substantially if Mitotic Arrest Deficient 2 (MAD2, an essential mitotic spindle checkpoint pathway component) is down-regulated [307].

4.7. NF-kappaB

Up-regulation of expression of antiapoptotic factors by NF-kappaB may antagonize cisplatin-induced apoptosis [242,308,309], and cisplatin significantly increases NF-kappaB DNA binding activity [310,311]. NF-kappaB inhibitors augment platinum activity against some cancer cell lines [60,311–322] and tumor xenograft models [310], but not against normal cells [311,312] nor against some other cancer cell lines [311,314]. NF-kappaB activation actually augmented cisplatin efficacy in some lines [323,324], or antagonized apoptosis with low cisplatin concentrations but enhanced efficacy of higher cisplatin concentrations [325].

4.8. Other transcription factors

Other transcription factors that may contribute to DNA repair and cisplatin resistance include Y-box-binding-protein-1 (YB-1), CCAAT-binding-transcription-factor-2 (CTF2), activating-transcription-factor-4 (ATF4), zinc-finger-factor-143 (ZNF143), mitochondrial-transcription-factor-A (mtTFA) [326], Ets-1 [327], AP-2 [182] and a protein related to zipper transcriptional factor [328]. YB-1 nuclear localization was increased in resistant cells [329]. Ets-1 [327] and AP-2 transcription factors (which are modulated by PKA) [182] contribute to transcriptional activation of other resistance genes including metallothioneins and DNA repair enzymes, and Ets-1 overexpression is associated with poor prognosis [327]. OC cell transfection with the splicing factor SPF45 (RBM17) also conferred resistance to carbo-platin [330].

4.9. Chromosomal alterations

Platinum-resistant cells may have several chromosomal abnormalities [331–338]. Telomere length, telomerase activity, and telomerase mRNA expression were reduced in cisplatin-resistant OC cell lines [339], and OCs with a loss of microsatellite D6S1581 were cisplatin-resistant [340].

4.10. Miscellaneous

Cells with pleiotropic drug resistance may also have altered metabolic pathways, with low mitochondrial membrane potential, increased fatty acid use for mitochondrial oxygen consumption, and high levels of mitochondrial-uncoupling-protein-2 [341]. Cisplatin-resistant cells also may have ultrastructural changes [342], with increased Golgi apparatus and mitochondria, and altered nuclear structure [130,343]

4.11. Gene arrays

Carboplatin-resistant versus -sensitive OC cells differentially expressed genes associated with apoptosis, cell–cell communication, cell adhesion, DNA repair, and cell proliferation [344]. In tumors from OC patients, the genes FN1, TOP2A, LBR, ASS, COL3A1, STK6, SGPP1, ITGAE, and PCNA correlated with platinum resistance [345]. Cisplatin-resistant SCCHN cell lines had up-regulated expression of ATP-binding cassette transporter genes (MDR1, MRP1, and MRP2), CD55, and PGK1 and down-regulated Caveolin 1 expression [80].

4.12. Proteomics

In proteomic analyses of cervix carcinoma cells, cisplatin-sensitive versus -resistant lines differentially expressed several proteins, including molecular chaperones (e.g., HSP60, HSP90, heat-shock cognate 71 kDa protein), calcium-binding proteins (e.g., calmodulin, calumenin), proteins involved in drug detoxification (e.g., the peroxiredoxins PRX 2 and PRX 6, and GST), anti-apoptotic proteins (e.g., 14-3-3) and ion channels (e.g., voltage-dependent anion-selective channel-1) [346]. Cisplatin exposure was associated with up-regulation of HSP60 and HSP90, 14-3-3 protein, GST in sensitive cells and PRX6 in resistant cells [346]. The study suggested a constitutive expression of defense factors by resistant cells, with further increase in expression upon cisplatin exposure [346].

5. Summary

It is unknown which of these numerous resistance mechanisms are most important clinically. NSCLC DRCs flatten at higher doses for cisplatin combinations, suggesting therapy efficacy is ultimately limited by exhaustion of a required factor [12], and this may also apply to other epithelial malignancies. Several clinical observations suggest epigenetic factors play a major role in resistance [6], and platinum resistance has been reported with down regulation of expression (e.g., by gene hypermethylation) of a variety of factors, including membrane transporters, hMLH1, and caspases [67,207,222,238]. In addition, when tumors shrink with chemotherapy, some patients have rapid tumor regrowth, while others have prolonged stability after therapy completion. Based on several observations, we propose the following model of resistance: cells with sufficient active resistance mechanisms [11] to withstand initial chemotherapy will continue to divide between therapy cycles. If active resistance mechanisms are insufficient for protection, non-cycling cells will nevertheless survive based on their intrinsic saturable passive resistance. Cells that do not have sufficient active resistance mechanisms to permit continued growth would down-regulate growth and remain quiescent until treatment cessation. While increasing drug doses

could overcome active resistance, the larger problem may remain identification of exploitable targets in non-cycling cells.

Reviewers

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Biography

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