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Novel Strategies for Reversing Platinum Resistance

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Abstract

Platinum based drugs continue to be the mainstay of therapy for ovarian cancer. Along with adverse effects, chemoresistance (intrinsic or acquired) has become a major limitation in the management of recurrent disease. Even though much is known about the effects of platinum drugs on cancer cells, the mechanisms underlying resistance are poorly understood. In this review, we summarize the current data on chemoresistance and discuss novel strategies to reverse resistance to platinum-based drugs. The most important targets highlighted here include Aurora kinases, PARP, ATP7B, and ERCC1. Furthermore, we discuss the implications of these novel approaches for ovarian cancer treatment.

Keywords

ATP7B; Cisplatin; Chemoresistance; Drug transport; Kinases; MK-0457; Ovarian cancer; siRNA; Tumor stroma; BRCA1

1. Introduction

Epithelial ovarian cancer is initially responsive to platinum-based therapy; however, recurrent disease is often refractory to treatment and is associated with high mortality rates (McGuire et al., 1996; Ozols and Young, 1984; Sood and Buller, 1998). It has been more than three decades since the discovery of the anticancer activity of cisplatin (Gottlieb and Drewinko, 1975; Rosenberg et al., 1965; Rosenberg et al., 1969), but we are just starting to discover the

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mechanisms that cause resistance. Platinum based drugs generally work by forming intra- or inter-strand cross-links in DNA that begins the process of cell-cycle arrest and results in tumor cell apoptosis (Kartalou and Essigmann, 2001; Pinto and Lippard, 1985). However, once the DNA is damaged, repair mechanisms are triggered resulting in improved cell survival (Brabec and Kasparkova, 2005).

Mechanisms that underlie platinum resistance are poorly understood, and are most likely multifactorial in origin (Agarwal and Kaye, 2003; Perez, 1998; Richardson and Kaye, 2005; Stewart, 2007; Vasey, 2003; Stordal and Davey, 2009). Broadly, resistance to anticancer platinum agents can be classified into two categories (Fojo and Bates, 2003; Stewart, 2007): first, due to inadequate delivery, platinum compounds may not reach intracellular levels needed for response. For example, poor or altered vascularization (van Hensbergen et al., 2004), reduced uptake, enhanced efflux of drug from endothelium, or increased metabolism of drugs in the tumor cell may all compromise drug levels in the tumor. Second, increased DNA damage repair mechanisms or prevention of apoptosis may lead to increased viability, and hence resistance (Figure 1).

Early on, it became evident that resistance to cis-platinum and nephrotoxicity will present as major obstacles in achieving sustainable responses. Therefore, studies started to focus on genetic and molecular mechanisms that mediate resistance. Recently, the role of microenvironment, especially, of extracellular matrix in platinum resistance is being explored and novel targets are being identified (Sherman-Baust et al., 2003; Morin, 2003). Additionally, the ability to identify new genes and proteins involved in drug resistance and to silence them using RNA interference (RNAi), small molecule inhibitors or specific antibodies offers hopes for reversing platinum resistance (Mangala et al., 2009). In this review, we will focus on some of these approaches, including those related to RNAi.

2. Strategies for Reversing Platinum Resistance

2.1. Targeting the tumor microenvironment

A decade ago, Sethi et al. reported that the extracellular matrix (ECM) protects tumor cells from chemotherapy induced apoptosis (Sethi et al., 1999). The interactions between the tumor cells and the stroma may result in conditions that generate favorable ECM interactions for protecting tumor cells from chemotherapy induced apoptosis (Hazlehurst and Dalton, 2001; Sethi et al., 1999; Meads et al., 2009). One of the critical fallouts of these interactions is the reorganization of the ECM in chemotherapy resistance. Sherman-Baust and colleagues reported that production of collagen VI by the tumor cells results in resistance to therapy (Sherman-Baust et al., 2003). In this study, many of the genes increased in the resistant cells were related to ECM. For example, COL6A3 was one of the most expressed genes. Propagation of cisplatin-sensitive cells in collagen VI containing conditions prompted resistance to platinum-based treatment. Staining of tumors with collagen VI antibody not only confirmed its expression, but also suggested reorganization of ECM around the tumor. Such remodeling may promote tumor cell survival when targeted with chemotherapeutic agents. Therefore, components of the ECM may represent novel targets for cancer therapy. Given the absence of conventional approaches to address many novel targets, RNAi may represent a promising new strategy. Landen and colleagues have demonstrated successful delivery of non-targeted small-interfering RNA (siRNA) incorporated into nanoparticles (neutral liposomal-DOPC) in orthotopic mouse models of ovarian carcinoma (Landen et al., 2005). More recently, Pan and associates applied quantitative proteomic approaches and analyzed tumor tissues that were harvested during primary cytoreductive surgery prior to the start of chemotherapy (Pan et al., 2009). They identified 44 proteins that were overexpressed and 34 proteins that had lower expression in chemosensitive compared to chemoresistant tumors. More than 25% of the

overexpressed proteins belonged to the ECM. Expression of these proteins may be useful for assessing and following response to therapy.

2.2. Nucleotide excision repair pathway

Nucleotide excision repair is highly conserved and plays an instrumental role in mediating resistance to platinum compounds (Rabik and Dolan, 2007). Lesions that result in alterations in the helical structure of the DNA or interfere with its replication and transcription are repaired by this pathway. The excision repair cross-complementation group1 (ERCC1) is a protein that plays a major role in mediating nucleotide excision repair. The complex dimerization of ERCC1 with pigmentosum complementation group F is required to excise the damaged DNA. *In vitro* exposure to cisplatin has been shown to result in platinum resistance and was associated with increased ERCC1 expression (Ferry et al., 2000). Additionally, ovarian cancer cell lines known to be resistant to platinum compounds had increased sensitivity after silencing ERCC1 expression using RNA interference (Selvakumaran et al., 2003). Chen and coworkers report that DNA hypermethylation of the ERCC1 promoter was inversely correlated to its mRNA expression and this association resulted in enhanced cisplatin chemosensitivity in a cohort of 32 glioma samples (Chen et al., 2009). ERCC1 mRNA levels evaluated in tumors from patients in clinical trials of non-small cell lung (Lord et al., 2002), colorectal (Shirota et al., 2001), and ovarian cancers (Kang et al., 2006) also showed an inverse association with survival or response to platinum compounds. Interestingly, clear cell ovarian carcinoma (known to have poor prognosis and being relatively platinum resistant) has significantly higher ERCC1 levels (Reed et al., 2003), which may reflect its role in protection from chemotherapy. Among 101 ovarian cancer patients who received carboplatin-paclitaxel combination therapy, almost 14% of the tumors had positive expression of ERCC1 (Steffensen et al., 2009). Seventy-five percent of the patients with chemoresistant cancer had positive ERCC1 expression in the tumor compared to 27% with negative expression. Additionally, ERCC1 expression was inversely correlated with progression-free survival. These findings offer opportunities to utilize RNAi or other approaches to target ERCC1 in patients that are prone to have resistance to platinum-based compounds to enhance therapeutic response.

2.3. Poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor combinations

In cells, DNA is constantly subjected to damage, however, many pathways work in a synchronized effort to repair the damage and preserve genomic integrity, thereby leading to improved cell survival (Hoeijmakers, 2001; Jackson, 2001; Lindahl, 1993). PARPs make up a large family of multifunctional enzymes and the most abundant enzyme in this group is PARP1. Playing a major role in repair of single strand DNA breaks, PARP1 repairs base excisions (Ame et al., 2004; Dantzer et al., 2000). Inactivity of PARP1 results in accumulation of single strand DNA breaks, eventually leading to double strand breaks. Homologous-recombination double-strand DNA repair pathway normally repairs these breaks and BRCA1 and BRCA2 are the key components of this repair mechanism. Rottenberg and colleagues reported a genetically engineered mouse model (GEMM) for BRCA1 associated breast cancer (Rottenberg et al., 2008; Borst et al., 2008) where the combination of a PARP inhibitor (AZD2281) with cisplatin or carboplatin resulted in increased recurrence-free and overall survival. In this study, PARP inhibition potentiated the effects of DNA damaging agents.

Sakai and colleagues have recently reported secondary mutations as a mechanism of cisplatin resistance in tumors that have BRCA2 mutations (Sakai et al., 2008; Sakai et al., 2009). They demonstrated that the acquired resistance to cisplatin was secondary to restoration of the wild-type BRCA2 reading frame. Additionally, Swisher and associates reported that in ovarian tumors that contain BRCA1 mutations, secondary mutations in BRCA1 can also mediate resistance to platinum-based therapy (Swisher et al., 2008). These reports demonstrate that BRCA1/2 mutations that are known to predispose to cancer also play a vital role in determining

clinical response to therapy. They suggest that restoration of these genes results in augmented repair of the DNA damage caused by platinum compounds, which contributes to chemoresistance.

To date, there are over 30 ongoing or recently completed studies that are evaluating PARP inhibition in combination with several different chemotherapeutic agents. Fong and coworkers reported a phase 1 trial of the PARP1 inhibitor, olaparib (AZD2281), in patients with specific DNA-repair defects, including those with BRCA1 or BRCA2 mutations. In this dose escalation study, 60 patients with advanced solid tumors were enrolled and treated with olaparib 10 mg daily to 600 mg twice daily. Additionally, a cohort of 22 patients who were carriers of BRCA1 or BRCA2 mutations were treated with olaparib at a dose of 200 mg twice daily. PARP1 inhibition was greater then 90% compared with baseline values. In patients with BRCA1 or BRCA2 mutations, 63% of the patients had clinical benefit and stabilization of disease (Fong et al., 2009).

2.4. Targeting the Aurora family of kinases

Aurora kinases play essential functions in mitotic integrity and cell cycle (Carvajal et al., 2006; Harrington et al., 2004; Katayama et al., 2003; Keen and Taylor, 2004). Landen and colleagues reported that Aurora-A is overexpressed in 83% of human epithelial ovarian cancers and predicts poor clinical outcome (Landen et al., 2007). Aurora-A kinase has also been implicated in protecting cells from apoptosis induced by chemotherapeutic agents such as cisplatin and paclitaxel by activation of AKT and checkpoint dysregulation (Anand et al., 2003; Yang et al., 2006). Sun and associates have recently demonstrated that inhibition of Aurora kinase can sensitize cells to chemotherapy by down-regulating NF-κB (Sun et al., 2007).

In a recent study, Lin and associates tested the effects of a pan-Aurora kinase inhibitor, MK-0457, in both platinum sensitive and resistant mouse models (Lin et al., 2008). Aurora kinase inhibition in the platinum-resistant A2780-cp20 model as monotherapy resulted in 78% reduction, and in combination with cisplatin resulted in 92% reduction in tumor growth compared to control. Furthermore, cisplatin plus MK-0457 treatment resulted in 91% reduction in tumor growth compared with cisplatin therapy alone. Combination of the Aurora kinase inhibitor and cisplatin significantly reduced tumor metastasis compared to cisplatin alone. These data were supported by favorable changes in the tumor microenvironment (tumor cell proliferation and apoptosis) that resulted from the addition of MK-0457. Additionally, therapeutic inhibition of Aurora kinases in taxane-resistant orthotopic models resulted in reduced tumor growth, which was related to increased apoptosis. This further emphasizes apoptosis as a key anti-tumor mechanism of Aurora kinase inhibition. Interestingly, several protease-related genes (CPB1, CTRB1 and ELA2A) were found to have increased expression in response to therapy. Increased expression of these degenerative genes may also be important in decreasing tumor growth. Recently, Kiat and coworkers described an Aurora-A kinase interacting protein (AIP) that works as an endogenous negative regulator of Aurora-A kinase (Kiat et al., 2002). Here, authors showed specificity and efficacy of Aurora-A down-regulation that is proteasome-dependent; however, the clinical potential of this pathway remains to be demonstrated.

There is growing interest in the role of Aurora kinases in chemoresistance. In pancreatic cancer models, Aurora-A kinase silencing with siRNA enhanced paclitaxel sensitivity (Hata et al., 2005). MK-0457 reported by Lin and associates also has high specificity for Aurora kinase (Lin et al., 2008). This study demonstrated potent antitumor activity in platinum-resistant orthotopic ovarian cancer models. The mechanisms described in this study provide the preclinical rationale for clinical trials focusing on targeting Aurora kinase.

2.5. Targeting platinum transport mechanisms

Recent data indicate that copper uptake and efflux transporter may also regulate the cellular pharmacodynamics of cisplatin (Katano et al., 2003; Ooi et al., 1996). In particular, ATP7A and ATP7B (copper transporters) have higher expression levels in platinum-resistant cells (Katano et al., 2002; Katano et al., 2004; Qian et al., 1995; Samimi et al., 2004). These copper transporters have also been functionally implicated in resistance to several platinum compounds, including cisplatin, carboplatin and oxaliplatin (Samimi et al., 2004). Among the solid tumors, ATP7B is shown to be overexpressed in several tumor types including gastric, breast, esophageal, hepatocellular, colorectal, uterine, and oral squamous cell carcinomas (Higashimoto et al., 2003; Kanzaki et al., 2002; Miyashita et al., 2003; Nakayama et al., 2004; Ohbu et al., 2003; Sugeno et al., 2004). Primary function of ATP7A and ATP7B is to transport copper into the lumen of trans-Golgi network (TGN) to facilitate biosynthesis of copper-dependent enzymes. The copper transporters also facilitate export of excess copper by sequestering copper into exocytic vesicles (Lutsenko et al., 2007). Cu-ATPases are known to bind copper at their NH_2-terminal domain and transfer copper across cell membranes using energy generated by ATP hydrolysis. Interestingly, elevated copper levels induce Cu-ATPase activity, leading to intracellular trafficking of ATP7A and ATP7B from the TGN to exocytic vesicles.

Until recently, the ability to target the transporters involved in cisplatin chemoresistance was limited. Mangala and colleagues have now utilized RNAi approaches to specifically target a key cisplatin resistance gene (ATP7B). First, using quantitative real-time RT-PCR, higher ATP7B expression levels were reported in platinum-resistant cells compared with sensitive cell lines (Mangala et al., 2009). They further showed that *in vitro* targeting ATP7B using RNAi approaches resulted in a 2.5-fold reduction in the IC_{50} levels of cisplatin and there was a 30% increase in DNA adduct formation in cisplatin-resistant cells. This may represent enhanced nuclear availability of cisplatin in cells where ATB7B was specifically targeted. Additionally, a highly efficient method for systemic delivery of siRNA was utilized (Halder et al., 2006; Landen et al., 2005), and demonstrated a 70–80% reduction in tumor growth when cisplatin therapy was combined with ATP7B gene silencing in orthotopic mouse models of ovarian carcinoma known to be resistant to cisplatin (A2780-CP20). The anti-tumor activity was accompanied by reductions in proliferation, cell survival, and angiogenesis. Leonhardt and colleagues (Leonhardt et al., 2009) provided additional evidence that supports the role of the NH_2-terminal metal binding domain in functional interactions between cisplatin and ATP7B. Data in this study provide a new understanding of cisplatin resistance in cancer cells and may have implications for therapeutic reversal of drug resistance.

3. Conclusion

One of the major obstacles to achieving the desired responses to treatment is resistance to therapy. In this review, we have summarized current data on cisplatin resistance and have described novel strategies that may be effective in reversing cisplatin resistance. Particularly, the potential benefits of targeting ATP7B using RNAi approaches, targeting Aurora family of kinases using small molecule inhibitors as well as PARP inhibitor combinations are discussed (see Table 1). These are promising targets that may hold the key to reversing platinum resistance in patients and should be explored further. Some of the targets involved in chemoresistance, however, may also play normal physiological functions. Therefore, therapeutic strategies aimed at reversing resistance should be pursued with caution to avoid potential toxicities.

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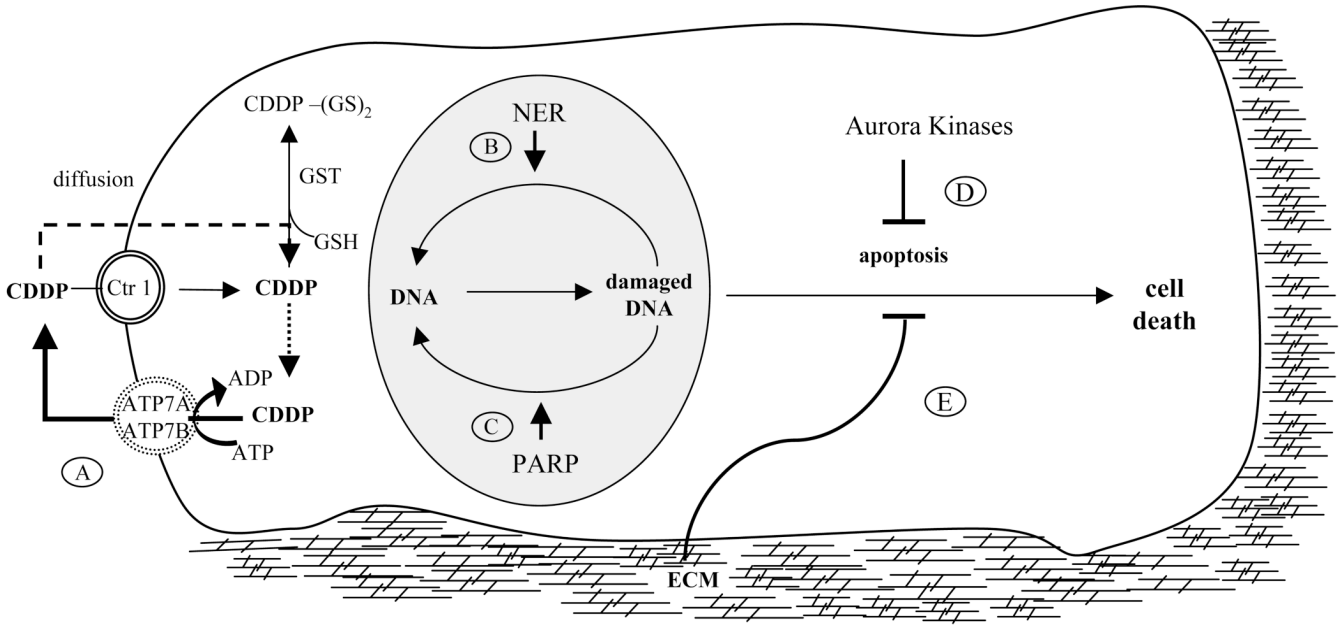

Fig. 1. Mechanisms of platinum resistance in cancer cells

Cisplatin (CDDP) enters cell by Ctr1 or diffusion and leads to DNA damage and cell death. Cisplatin resistance may evolve through the following pathways: A) cisplatin can be pumped out of the cell by ATP7B. B) Nucleotide excision repair pathway (NER) and C) PARP repair of DNA damage. D) Aurora kinases may protect cells against chemotherapy by blocking apoptosis; E) ECM produces favorable changes in tumor microenvironment that inhibit chemotherapy-induced apoptosis

Table1

Current studies exploring reversal of cisplatin resistance by targeting PARP, Aurora Kinase, ERCC1 or ATP7B

Target	Model	Study Design	Compound	Target/use	Reference
PARP	Ovarian	Phase II	KU-0059436	PARP inhibition	www.clinicaltrials.gov
IGF1R	Ovarian	Preclinical	BMS-536924	PARPI sensitization	(Beauchamp et al., 2009)
PARP	Ovarian	Phase I	AZD2281	BRCA mutation	(Fong et al., 2009)
PARP	Breast	Preclinical	AZD2281	BRCA2 mutation/P53	(Hay et al, 2009)
PARP	Triple (−) Breast cancer	Phase II	BSI201	PARP inhibition	www.clinicaltrials.gov
Aurora Kinase	Tumor cell lines	Preclinical	R763/AS703569	Anti-tumor activity	(McLaughlin et al., 2009)
Aurora Kinase	Ovarian	Preclinical	MK-0457	Reversal of platinum resistance	(Mangala et al., 2009)
Aurora Kinase	Multiple	Preclinical	SNS-314	Anti-tumor activity	(Arbitrario et al., 2009)
Multikinase	Leukemia	Preclinical	KW-2449	Anti-tumor activity	(Shiotsu et al., 2009)
ERCC1	No data	No data	-	-	-
ATP7B	Ovarian	Preclinical	siRNA/DOPC	Reversal of platinum resistance	(Mangala et al., 2009)